



DIRECTOR'S REPORT

to the

National Advisory Council on Drug Abuse

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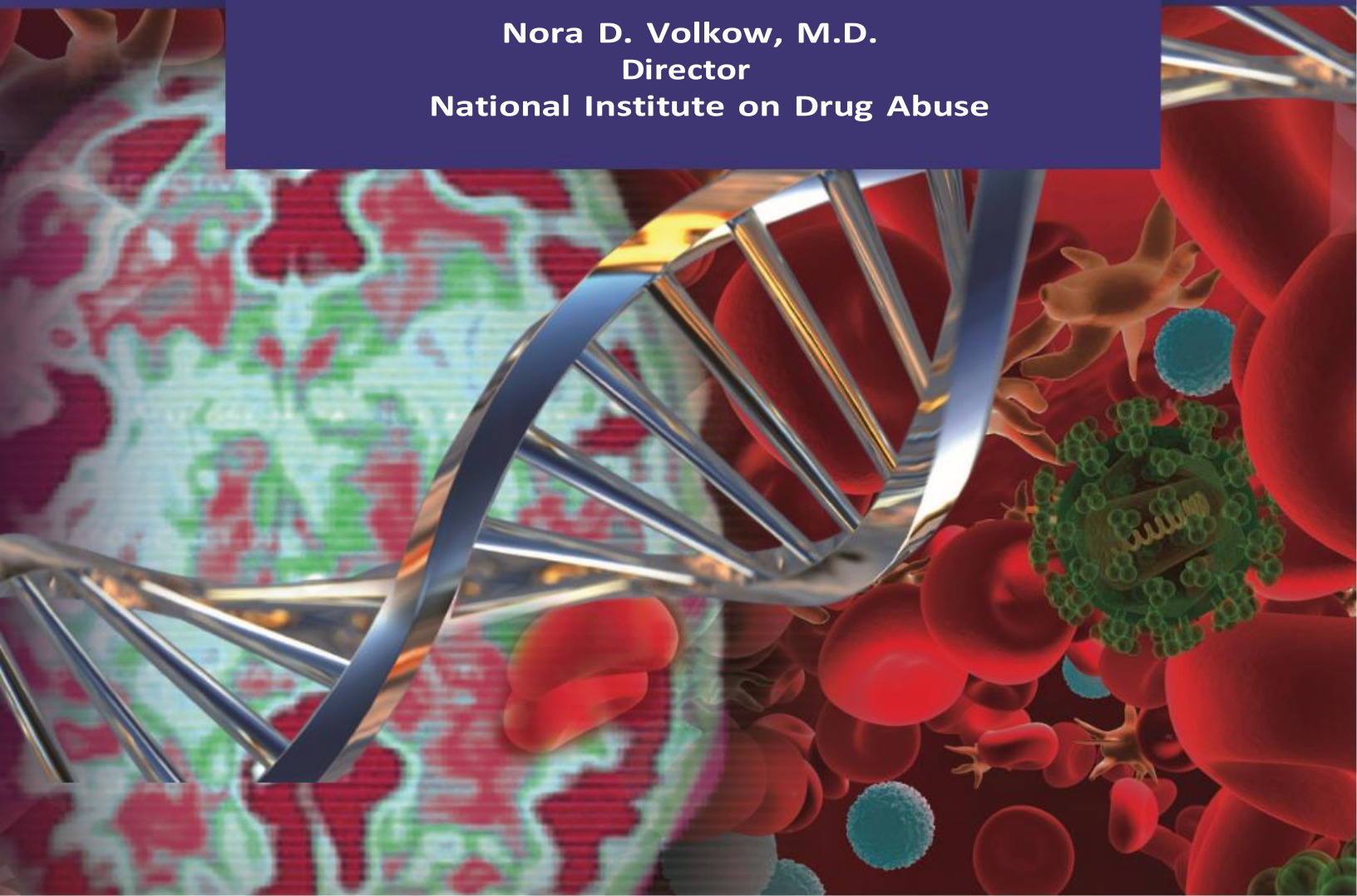


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RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH

[Prenatal Opioid Exposure Inhibits Microglial Sculpting Of The Dopamine System Selectively In Adolescent Male Offspring](#) Smith CJ, Lintz T, Clark MJ, Malacon KE, Abiad A, Constantino NJ, Kim VJ, Jo YC, Alonso-Caraballo Y, Bilbo SD, Chartoff EH. *Neuropsychopharm.* 2022; 47(10): 1755-1763.

The current opioid epidemic has dramatically increased the number of children who are prenatally exposed to opioids, including oxycodone. A number of social and cognitive abnormalities have been documented in these children as they reach young adulthood. However, little is known about the mechanisms underlying developmental effects of prenatal opioid exposure. Microglia, the resident immune cells of the brain, respond to acute opioid exposure in adulthood. Moreover, microglia are known to sculpt neural circuits during typical development. Indeed, we recently found that microglial phagocytosis of dopamine D1 receptors (D1R) in the nucleus accumbens (Nac) is required for the natural developmental decline in Nac-D1R that occurs between adolescence and adulthood in rats. This microglial pruning occurs only in males and is required for the normal developmental trajectory of social play behavior. However, virtually nothing is known as to whether this developmental program is altered by prenatal exposure to opioids. Here, we show in rats that maternal oxycodone self-administration during pregnancy leads to reduced adolescent microglial phagocytosis of D1R and subsequently higher D1R density within the Nac in adult male, but not female, offspring. Finally, we show prenatal and adult behavioral deficits in opioid-exposed offspring, including impaired extinction of oxycodone-conditioned place preference in males. This work demonstrates for the first time that microglia play a key role in translating prenatal opioid exposure to changes in neural systems and behavior.

[Chromatin Architecture In Addiction Circuitry Identifies Risk Genes And Potential Biological Mechanisms Underlying Cigarette Smoking And Alcohol Use Traits](#) Sey NYA, Hu B, Iskhakova M, Lee S, Sun H, Shokrian N, Ben Hutta G, Marks JA, Quach BC, Johnson EO, Hancock DB, Akbarian S, Won H. *Mol Psychiatry*; 2022; 27(7): 3085-3094.

Cigarette smoking and alcohol use are among the most prevalent substances used worldwide and account for a substantial proportion of preventable morbidity and mortality, underscoring the public health significance of understanding their etiology. Genome-wide association studies (GWAS) have successfully identified genetic variants associated with cigarette smoking and alcohol use traits. However, the vast majority of risk variants reside in non-coding regions of the genome, and their target genes and neurobiological mechanisms are unknown. Chromosomal conformation mappings can address this knowledge gap by charting the interaction profiles of risk-associated regulatory variants with target genes. To investigate the functional impact of common variants associated with cigarette smoking and alcohol use traits, we applied Hi-C coupled MAGMA (H-MAGMA) built upon cortical and newly generated midbrain dopaminergic neuronal Hi-C datasets to GWAS summary statistics of nicotine dependence, cigarettes per day, problematic alcohol use, and drinks per week. The identified risk genes mapped to key pathways associated with cigarette smoking and alcohol use traits, including drug metabolic processes and neuronal apoptosis. Risk genes were highly expressed in cortical glutamatergic, midbrain dopaminergic, GABAergic, and serotonergic neurons, suggesting them as relevant cell types in understanding the mechanisms by which genetic

risk factors influence cigarette smoking and alcohol use. Lastly, we identified pleiotropic genes between cigarette smoking and alcohol use traits under the assumption that they may reveal substance-agnostic, shared neurobiological mechanisms of addiction. The number of pleiotropic genes was ~26-fold higher in dopaminergic neurons than in cortical neurons, emphasizing the critical role of ascending dopaminergic pathways in mediating general addiction phenotypes. Collectively, brain region- and neuronal subtype-specific 3D genome architecture helps refine neurobiological hypotheses for smoking, alcohol, and general addiction phenotypes by linking genetic risk factors to their target genes.

Bayesian Causal Network Modeling Suggests Adolescent Cannabis Use Accelerates Prefrontal Cortical Thinning

Owens MM, Albaugh MD, Allgaier N, Yuan D, Robert G, Cupertino RB, Spechler PA, Juliano A, Hahn S, Banaschewski T, Bokde Arun LW, Desrivières S, Flor H, Grigis A, Gowland P, Heinz A, Brühl R, Martinot J-L, Martinot M-L P, Artiges E, Nees F, Orfanos DP, Lemaitre H, Paus T, Poustka L, Millenet S, Fröhner JH, Smolka MN, Walter H, Whelan R Mackey S, Schumann G, Garavan H, IMAGEN Consortium. *Transl Psychiatry*. 2022; 12(1): 188.

While there is substantial evidence that cannabis use is associated with differences in human brain development, most of this evidence is correlational in nature. Bayesian causal network (BCN) modeling attempts to identify probable causal relationships in correlational data using conditional probabilities to estimate directional associations between a set of interrelated variables. In this study, we employed BCN modeling in 637 adolescents from the IMAGEN study who were cannabis naïve at age 14 to provide evidence that the accelerated prefrontal cortical thinning found previously in adolescent cannabis users by Albaugh et al., 2021 is a result of cannabis use causally affecting neurodevelopment. BCNs incorporated data on cannabis use, prefrontal cortical thickness, and other factors related to both brain development and cannabis use, including demographics, psychopathology, childhood adversity, and other substance use. All BCN algorithms strongly suggested a directional relationship from adolescent cannabis use to accelerated cortical thinning. While BCN modeling alone does not prove a causal relationship, these results are consistent with a body of animal and human research suggesting that adolescent cannabis use adversely affects brain development.

Adolescent Sleep Shapes Social Novelty Preference In Mice Bian W-J, Brewer CL, Kauer JA, de Lecea L. *Nat Neurosci*. 2022; 25(7): 912-923.

Sleep disturbances frequently occur in neurodevelopmental disorders such as autism, but the developmental role of sleep is largely unexplored, and a causal relationship between developmental sleep defects and behavioral consequences in adulthood remains elusive. Here, we show that in mice, sleep disruption (SD) in adolescence, but not in adulthood, causes long-lasting impairment in social novelty preference. Furthermore, adolescent SD alters the activation and release patterns of dopaminergic neurons in the ventral tegmental area (VTA) in response to social novelty. This developmental sleep function is mediated by balanced VTA activity during adolescence; chemogenetic excitation mimics, whereas silencing rescues, the social deficits of adolescent SD. Finally, we show that in Shank3-mutant mice, improving sleep or rectifying VTA activity during adolescence ameliorates adult social deficits. Together, our results identify a critical role of sleep and dopaminergic activity in the development of social interaction behavior.

[In Situ Identification Of Cellular Drug Targets In Mammalian Tissue](#) Pang Z, Schafroth MA, Ogasawara D, Wang Y, Nudell V, Lal NK, Yang D, Wang K, Herbst DM, Ha J, Guijas C, Blankman JL, Cravatt BF, Ye L. *Cell*. 2022; 185(10): 1793-1805.

The lack of tools to observe drug-target interactions at cellular resolution in intact tissue has been a major barrier to understanding in vivo drug actions. Here, we develop clearing-assisted tissue click chemistry (CATCH) to optically image covalent drug targets in intact mammalian tissues. CATCH permits specific and robust in situ fluorescence imaging of target-bound drug molecules at subcellular resolution and enables the identification of target cell types. Using well-established inhibitors of endocannabinoid hydrolases and monoamine oxidases, direct or competitive CATCH not only reveals distinct anatomical distributions and predominant cell targets of different drug compounds in the mouse brain but also uncovers unexpected differences in drug engagement across and within brain regions, reflecting rare cell types, as well as dose-dependent target shifts across tissue, cellular, and subcellular compartments that are not accessible by conventional methods. CATCH represents a valuable platform for visualizing in vivo interactions of small molecules in tissue.

EPIDEMIOLOGY, PREVENTION, AND SERVICES RESEARCH

[Reddit Discussions About Buprenorphine Associated Precipitated Withdrawal In The Era Of Fentanyl](#) Spadaro A, Sarker A, Hogg-Bremer W, Love JS, O'Donnell N, Nelson LS, Perrone J. *Clin Toxicol (Phila)*. 2022; 60(6): 694-701.

Background: Induction of buprenorphine, an evidence-based treatment for opioid use disorder (OUD), has been reported to be difficult for people with heavy use of fentanyl, the most prevalent opioid in many areas of the country. In this population, precipitated opioid withdrawal (POW) may occur even after individuals have completed a period of opioid abstinence prior to induction. Our objective was to study potential associations between fentanyl, buprenorphine induction, and POW, using social media data. **Methods:** This is a mixed methods study of data from seven opioid-related forums (subreddits) on Reddit. We retrieved publicly available data from the subreddits via an application programming interface and applied natural language processing to identify subsets of posts relevant to buprenorphine induction, POW, and fentanyl and analogs (F&A). We computed mention frequencies for keywords/phrases of interest specified by our medical toxicology experts. We further conducted manual, qualitative, and thematic analyses of automatically identified posts to characterize the information presented. **Results:** In 267,136 retrieved posts, substantial increases in mentions of F&A (3 in 2013 to 3870 in 2020) and POW (2 in 2012 to 332 in 2020) were observed. F&A mentions from 2013 to 2021 were strongly correlated with mentions of POW (Spearman's ρ : 0.882; $p = .0016$), and mentions of the Bernese method (BM), a microdosing induction strategy (Spearman's ρ : 0.917; $p = .0005$). Manual review of 384 POW- and 106 BM-mentioning posts revealed that common discussion themes included "specific triggers of POW" (55.1%), "buprenorphine dosing strategies" (38.2%) and "experiences of OUD" (36.1%). Many reported experiencing POW despite prolonged opioid abstinence periods, and recommended induction via microdosing, including specifically via the BM. **Conclusions:** Reddit subscribers often associate POW with F&A use and describe self-managed buprenorphine induction strategies involving microdosing to avoid POW. Further objective studies in patients with fentanyl use and OUD initiating buprenorphine are needed to corroborate these findings.

[Copycat And Lookalike Edible Cannabis Product Packaging In The United States](#) Ompad DC, Snyder KM, Sandh S, Hagen D, Collier KJ, Goldmann E, Goodman MS, Tan ASL. Drug Alcohol Depend. 2022; 235: 109409.

Background: Recent media reports have highlighted copycat/lookalike cannabis edibles as a public health concern. No empirical papers have described this phenomenon. **Methods:** From May 2020-August 2021, we collected photos of cannabis products via an online survey of cannabis users and through personal contacts. Copycat/lookalike products are defined as those that use the same or similar brand name, logo, and/or imagery as an existing commercial non-cannabis counterpart (CNCC). We assessed each package for similarities with its CNCC with respect to brand name, product name, font, color, flavors, and brand/promotional characters. We examined cannabis content indicators including: THC content per package and serving, cannabis leaf symbol, product warnings, cannabis terms, cannabis motifs, activation time, and guidance on edible use. **Results:** We collected photos of 731 cannabis products; 267 (36%) were edibles of which 22 (8%) represented 13 unique copycat/lookalike products. Eight used exact brand/product names as existing CNCCs, and five used similar names. Packages copied or imitated a mean of 3.9 of six features and indicated cannabis content with a mean of 4.1 of eight features. Thirteen packages indicated a mean THC content of 459 mg/package. Four reported THC dose per serving, with a mean dose of 47.5 mg. **Conclusions:** Our content analysis highlights three key concerns. First, copycat/lookalike edibles subtly indicate cannabis content while using high fidelity replication or imitation of their CNCC. Second, THC content is high and there were multiple 10 mg THC doses in the equivalent of 1 serving of a CNCC. Third, these products may be attractive to children.

[Leveraging Technology To Address Unhealthy Drug Use In Primary Care: Effectiveness Of The Substance Use Screening and Intervention Tool \(SUSIT\)](#) McNeely J, Mazumdar M, Appleton N, Bunting AM, Polyn A, Floyd S, Sharma A, Shelley D, Cleland CM. Subst Abus. 2022; 43(1): 564-572.

Background: Screening for unhealthy drug use is now recommended for adult primary care patients, but primary care providers (PCPs) generally lack the time and knowledge required to screen and deliver an intervention during the medical visit. To address these barriers, we developed a tablet computer-based 'Substance Use Screening and Intervention Tool (SUSIT)'. Using the SUSIT, patients self-administer screening questionnaires prior to the medical visit, and results are presented to the PCP at the point of care, paired with clinical decision support (CDS) that guides them in providing a brief intervention (BI) for unhealthy drug use. **Methods:** PCPs and their patients with moderate-risk drug use were recruited from primary care and HIV clinics. A pre-post design compared a control 'screening only' (SO) period to an intervention 'SUSIT' period. Unique patients were enrolled in each period. In both conditions, patients completed screening and identified their drug of most concern (DOMC) before the visit and completed a questionnaire about BI delivery by the PCP after the visit. In the SUSIT condition only, PCPs received the tablet with the patient's screening results and CDS. Multilevel models with random intercepts and patients nested within PCPs examined the effect of the SUSIT intervention on PCP delivery of BI. **Results:** 20 PCPs and 79 patients (42 SO, 37 SUSIT) participated. Most patients had moderate-risk marijuana use (92.4%), and selected marijuana as the DOMC (68.4%). Moderate-risk use of drugs other than marijuana included cocaine (15.2%), hallucinogens (12.7%), and sedatives (12.7%). Compared to the SO condition, patients in SUSIT had higher odds of receiving any BI for drug use, with an adjusted odds ratio of 11.59 (95% confidence interval: 3.39, 39.25), and received

more elements of BI for drug use. **Conclusions:** The SUSIT significantly increased delivery of BI for drug use by PCPs during routine primary care encounters.

Collateral Benefits Of Evidence-Based Substance Use Prevention Programming During Middle-School On Young Adult Romantic Relationship Functioning

LoBraico EJ, Fosco GM, Fang S, Spoth R, Redmond C, Feinberg ME. *Prev Sci.* 2022; 23(4): 618-629.

The quality of romantic relationships formed during early adulthood has critical implications for physical and psychological wellbeing, future romantic relationships, and subsequent parenting of the next generation. The present study evaluates the cross-over effects of the PROSPER-delivered adolescent substance use prevention programming on young adult romantic relationship functioning through a long-term developmental cascade of adolescent skills and behaviors, along with subsequent family-of-origin functioning. Prospective, longitudinal, bivariate growth models were used to analyze the effects of the PROSPER-delivered interventions in a sample of 1008 youths living in rural and semi-rural communities in Iowa and Pennsylvania, starting in sixth grade ($Age_M = 11.8$; 62% female) who were in a steady romantic relationship at the young adult assessment ($Age_M = 19.5$). Findings indicated a cascading effect through which PROSPER promotes adolescent problem-solving skills during early-to-mid-adolescence; problem-solving skills were associated with better family functioning during mid-adolescence; and family functioning was associated with better romantic relationship quality, indicated by lower levels of relationship violence and more effective relationship problem-solving in young adulthood. PROSPER, which primarily targets adolescent substance misuse and conduct problem prevention, has lasting, collateral effects that benefit young adults in their romantic relationship functioning - which may have further downstream benefits for their own relationships and those of their children (i.e., intergenerational transmission effects). These findings add to the growing body of literature evidencing important cross-over effects of widely disseminated substance use prevention programs delivered during adolescence.

Estimating Naloxone Need In The USA Across Fentanyl, Heroin, And Prescription Opioid Epidemics: A Modelling Study

Irvine MA, Oller D, Boggis J, Bishop B, Coombs D, Wheeler E, Doe-Simkins M, Walley AY, Marshall BDL, Bratberg J, Green TC. *Lancet Public Health.* 2022; 7(3): e210-e218.

The US overdose crisis is driven by fentanyl, heroin, and prescription opioids. One evidence-based policy response has been to broaden naloxone distribution, but how much naloxone a community would need to reduce the incidence of fatal overdose is unclear. The study estimated state-level US naloxone need in 2017 across three main naloxone access points (community-based programmes, provider prescription, and pharmacy-initiated distribution) and by dominant opioid epidemic type (fentanyl, heroin, and prescription opioid). In this modelling study, the investigators developed, parameterized, and applied a mechanistic model of risk of opioid overdose and used it to estimate the expected reduction in opioid overdose mortality after deployment of a given number of two-dose naloxone kits. Need for naloxone differed by epidemic type, with fentanyl epidemics having the consistently highest probability of naloxone use during witnessed overdose events (range 58–76% across the three modelled states in this category) and prescription opioid-dominated epidemics having the lowest (range 0–20%). Overall, in 2017, community-based and pharmacy-initiated naloxone access points had higher probability of naloxone use in witnessed overdose and higher numbers of deaths averted per 100,000 people in state-specific results with these two access points than with provider-prescribed access only. To achieve a target of naloxone use in 80% of witnessed

overdoses, need varied from no additional kits (estimated as sufficient) to 1270 kits needed per 100,000 population across the 12 modelled states annually. In 2017, only Arizona had sufficient kits to meet this target. Opioid epidemic type and how naloxone is accessed have large effects on the probability of naloxone use, and the number of deaths due to overdose averted. The extent of naloxone distribution, especially through community-based programmes and pharmacy-initiated access points, warrants substantial expansion in nearly every US state.

TREATMENT RESEARCH

Maternal Nicotine Metabolism Moderates The Impact Of Maternal Cigarette Smoking On Infant Birth Weight: A Collaborative Perinatal Project Investigation Stroud LR, Papandonatos GD, Jao NC, Niaura R, Buka S, Benowitz NL. *Drug Alcohol Depend.* 2022; 233: 109358.

BACKGROUND: Maternal cigarette smoking is an important modifiable risk factor for low birth weight in the US. We investigated the maternal nicotine metabolite ratio (NMR; trans-3'-hydroxycotinine/cotinine) - a genetically-informed biomarker of nicotine clearance - as a moderator of links between prenatal cigarette use and birth weight. We also explored the role of race in these associations. **METHODS:** Participants were 454 pregnant women (Mage = 25 years; 11% Black) who smoked cigarettes and their 537 infants from the Collaborative Perinatal Project. Cigarettes smoked per day were assessed at each prenatal visit; maternal NMR was assayed from third trimester serum. Birth weight was obtained from medical records. Generalized estimating equations were used to evaluate associations between cigarette smoking, NMR, race, and birth weight.

RESULTS: NMR moderated continuous associations between cigarettes per day over pregnancy and infant birth weight ($p = .025$). Among women who smoked at moderate levels (<15 cigarettes per day), those with slower NMR showed ~50-100 g decrements in birth weight versus those with faster NMR., while there were no significant associations between NMR and birth weight among women who smoked 15+ cigarettes per day. Although effects of NMR on birthweight were similar for Black and white women, Black women showed significantly slower NMR ($p < .001$).

CONCLUSIONS: This is the first demonstration that the maternal nicotine metabolism phenotype moderates associations between maternal smoking during pregnancy and birth weight. Infants of women with slower nicotine metabolism - including disproportionate representation of Black women - may be at heightened risk for morbidity from maternal smoking.

Effects Of Acute And Repeated Administration Of The Selective M4 PAM VU0152099 On Cocaine Versus Food Choice In Male Rats Thomsen M, Crittenden JR, Lindsley CW, Graybiel, AM. *Addict Biol.* 2022; 27(2): e13145.

Ligands that stimulate muscarinic acetylcholine receptors 1 and 4 (M1, M4) have shown promising effects as putative pharmacotherapy for cocaine use disorder in rodent assays. We have previously shown reductions in cocaine effects with acute M4 stimulation, as well as long-lasting, delayed reductions in cocaine taking and cocaine seeking with combined M1 /M4 receptor stimulation or with M1 stimulation alone. M4 stimulation opposes dopaminergic signaling acutely, but direct dopamine receptor antagonists have proved unhelpful in managing cocaine use disorder because they lose efficacy with long-term administration. It is therefore critical to determine whether M4 approaches themselves can remain effective with repeated or chronic dosing. We assessed the effects of repeated administration of the M4 positive allosteric modulator (PAM) VU0152099 in rats trained to choose between intravenous cocaine and a liquid food reinforcer to obtain

quantitative measurement of whether M4 stimulation could produce delayed and lasting reduction in cocaine taking. VU0152099 produced progressively augmenting suppression of cocaine choice and cocaine intake but produced neither rebound nor lasting effects after treatment ended.

To compare and contrast effects of M1 versus M4 stimulation, we tested whether the M4 PAM VU0152100 suppressed cocaine self-administration in mice lacking CalDAG-EFI signaling factor, required for M1 -mediated suppression of cocaine self-administration. CalDAG-GEFI ablation had no effect on M4 -mediated suppression of cocaine self-administration. These findings support the potential usefulness of M4 PAMs as pharmacotherapy to manage cocaine use disorder, alone or in combination with M1 -selective ligands, and show that M1 and M4 stimulation modulate cocaine-taking behaviour by distinct mechanisms.

Comparable Impairment Of Vascular Endothelial Function By A Wide Range Of Electronic Nicotine Delivery Devices Rao P, Han DD, Tan K, Mohammadi L, Derakhshandeh R, Navabzadeh M, Goyal N, Springer ML. Nicotine Tob Res. 2022; 24(7): 1055-1062.

INTRODUCTION: Electronic nicotine delivery systems (ENDS; ie, vaping devices) such as e-cigarettes, heated tobacco products, and newer coil-less ultrasonic vaping devices are promoted as less harmful alternatives to combustible cigarettes. However, their cardiovascular effects are understudied. We investigated whether exposure to aerosol from a wide range of ENDS devices, including a new ultrasonic vaping device, impairs endothelial function. **AIMS AND METHODS:** We measured arterial flow-mediated dilation (FMD) in rats (n = 8/group) exposed to single session of 10 cycles of pulsatile 5-second exposure over 5 minutes to aerosol from e-liquids with and without nicotine generated from a USONICIG ultrasonic vaping device, previous generation e-cigarettes, 5% nicotine JUUL pods (Virginia Tobacco, Mango, Menthol), and an IQOS heated tobacco product; with Marlboro Red cigarette smoke and clean air as controls. We evaluated nicotine absorption and serum nitric oxide levels after exposure, and effects of different nicotine acidifiers on platelet aggregation. **RESULTS:** Aerosol/smoke from all conditions except air significantly impaired FMD. Serum nicotine varied widely from highest in the IQOS group to lowest in USONICIG and previous generation e-cig groups. Nitric oxide levels were not affected by exposure. Exposure to JUUL and similarly acidified nicotine salt e-liquids did not affect platelet aggregation rate. Despite lack of heating coil, the USONICIG under airflow conditions heated e-liquid to ~77°C. **CONCLUSIONS:** A wide range of ENDS, including multiple types of e-cigarettes with and without nicotine, a heated tobacco product, and an ultrasonic vaping device devoid of heating coil, all impair FMD after a single vaping session comparably to combusted cigarettes. **IMPLICATIONS:** The need to understand the cardiovascular effects of various ENDS is of timely importance, as we have seen a dramatic increase in the use of these products in recent years, along with the growing assumption among its users that these devices are relatively benign. Our conclusion that a single exposure to aerosol from a wide range of ENDS impairs endothelial function comparably to cigarettes indicates that vaping can cause similar acute vascular functional impairment to smoking and is not a harmless activity.

Probing The Activity Of Mitragyna Speciosa (Kratom) Alkaloids At Serotonin G Protein-Coupled Receptors Chen Y, McCurdy C, Mottinelli M, Canal C. FASEB J. 2022; 36 Suppl 1. The nation's persistent opioid epidemic requires innovative treatment interventions. *Mitragyna speciosa*, or kratom, is an alkaloid-containing tropical plant that has emerged as a potential opioid substitute therapy in recent decades. There are, however, no FDA-approved uses for kratom, and scientists are actively engaged to elucidate the potential therapeutic benefits and harmful effects of kratom.

Studies of kratom alkaloids have mainly focused on their opioid receptor activity, but emerging data show kratom has physiologically-relevant activity at other biological targets. We recently reported that two kratom alkaloids prevalent in leaves of the kratom plant, speciogynine and paynantheine, bind to serotonin (5-HT) 5-HT_{1A}Rs and 5-HT_{2B}Rs with affinities (K_i) less ≤ 100 nM and that their 9-O-desmethyl metabolites are efficacious agonists at 5-HT_{1A}Rs (León et al., 2021 PMID: 34467758). We are undertaking studies to evaluate the pharmacology of the most prevalent alkaloids found in kratom leaves at each of the genetically-encoded 5-HT G protein-coupled receptors (GPCRs). To further elucidate 5-HT_{2B} G-protein transduction pathways modulated by kratom alkaloids, we are utilizing the TRUPATH biosensor platform. By evaluating the potency and efficacy of kratom alkaloids to modulate the activity of unique G alpha subtypes linked to 5-HT_{2B}Rs, we will provide fundamental 5-HT_{2B} pharmacological characteristics of kratom alkaloids. The 5-HT_{2B} is a crucial target for drug safety profiling since activation of this receptor can lead to cardiac valvulopathy. In addition, we are testing kratom alkaloids with an appreciable 5-HT_{2B} affinity for their potential mitogenic activity in HEK cells utilizing [³H]thymidine incorporation. This research will provide crucial information about kratom's pharmacological profile, independent of opioid receptors, that may contribute to its physiological effects.

[Novel Rapid-Acting Sublingual Nicotine Tablet As A Cigarette Substitution Strategy](#) Rose JE, Behm FM, Botts TL, Botts DR, Willette PN, Vocci F, McCarty J. *Psychopharmacology (Berl)*. 2022; 239(9): 2853-2862.

RATIONALE: Current nicotine replacement products provide a much slower onset of nicotine delivery than cigarettes, and hence are only marginally effective at supplanting cigarette smoking. Therefore, more effective forms of nicotine replacement are needed. **OBJECTIVES:** This initial investigation characterized the pharmacokinetic (PK) and subjective effects of a novel sublingual (SL) nicotine tablet designed to deliver nicotine more rapidly to the bloodstream of smokers.

METHODS: Study 1 (N = 6) characterized the pharmacokinetics of a 2 mg nicotine SL tablet in comparison to an FDA-approved, marketed 2 mg nicotine lozenge. Study 2 (N = 24) assessed subjective responses of smokers to a single use of a 1 mg and 2 mg SL tablet. **RESULTS:** Study 1 found that the time to maximum blood nicotine concentrations was significantly shorter for the SL tablet (14 min) than for the lozenge (82 min), and the initial rate of nicotine absorption was higher (0.4 ng/mL*min vs. 0.0 ng/mL*min), supporting the hypothesis that the SL tablet delivered nicotine more rapidly. Study 2 found that participants reported immediate relief of nicotine withdrawal symptoms after tablet administration, and craving reduction after the 2 mg tablet approached the degree reported for their usual brands of cigarettes (4.2 vs. 4.6 on a 7-point scale). Other subjective responses showed the tablet to be an appealing alternative to smoking. **CONCLUSIONS:** The novel SL tablet studied shows promise as a nicotine substitution strategy for tobacco harm reduction and smoking cessation treatment. Additional studies are warranted to further investigate the potential of this new approach.

[Recovery Of Dopaminergic System After Cocaine Exposure And Impact Of A Long-acting Cocaine Hydrolase](#) Deng J, Zhang T, Zheng X, Shang L, Zhan C-G, Zheng F. *Addict Biol*. 2022; 27(4): e13179.

Dysregulation of dopamine transporters (DAT) within the dopaminergic system is an important biomarker of cocaine exposure. Depending on cocaine amount in-taken, one-time exposure in rats could lead to most (>95% of total) of DAT translocating to plasma membrane of the dopaminergic neurons compared to normal DAT distribution (~5.7% on the plasma membrane). Without further

cocaine exposure, the time course of striatal DAT distribution, in terms of intracellular and plasma membrane fractions of DAT, represents a recovery process of the dopaminergic system. In this study, we demonstrated that after an acute cocaine exposure of 20 mg/kg (i.p.), the initial recovery process from days 1 to 15 in rats was relatively faster (from >95% on day 1 to ~35.4% on day 15). However, complete recovery of the striatal DAT distribution may take about 60 days. In another situation, with repeated cocaine exposures for once every other day for a total of 17 doses of 20 mg/kg cocaine (i.p.) from days 0 to 32, the complete recovery of striatal DAT distribution may take an even longer time (about 90 days), which represents a consequence of chronic cocaine use. Further, we demonstrated that a highly efficient Fc-fused cocaine hydrolase, Coch5-Fc(M6), effectively blocked cocaine-induced hyperactivity and DAT trafficking with repeated cocaine exposures by maintaining a plasma Coch5-Fc(M6) concentration $\geq 58.7 \pm 2.9$ nM in rats. The cocaine hydrolase protected dopaminergic system and helped the cocaine-altered DAT distribution to recover by preventing the dopaminergic system from further damage by cocaine.

[Consideration Of Sex And Gender Differences In Addiction Medication Response](#) McKee SA, McRae-Clark AL. *Biol Sex Differ.* 2022; 13(1): 34.

Substance use continues to contribute to significant morbidity and mortality in the United States, for both women and men, more so than another other preventable health condition. To reduce the public health burden attributable to substances, the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism have identified that medication development for substance use disorder is a high priority research area. Furthermore, both Institutes have stated that research on sex and gender differences in substance use medication development is a critical area. The purpose of the current narrative review is to highlight how sex and gender have been considered (or not) in medication trials for substance use disorders to clarify and summarize what is known regarding sex and gender differences in efficacy and to provide direction to the field to advance medication development that is consistent with current NIH 'sex as a biological variable' (SABV) policy. To that end, we reviewed major classes of abused substances (nicotine, alcohol, cocaine, cannabis, opioids) demonstrating that, sex and gender have not been well-considered in addiction medication development research. However, when adequate data on sex and gender differences have been evaluated (i.e., in tobacco cessation), clinically significant differences in response have been identified between women and men. Across the other drugs of abuse reviewed, data also suggest sex and gender may be predictive of outcome for some agents, although the relatively low representation of women in clinical research samples limits making definitive conclusions. We recommend the incorporation of sex and gender into clinical care guidelines and improved access to publicly available sex-stratified data from medication development investigations.

[Benzodiazepine-Involved Overdose Deaths In The USA: 2000-2019](#) Kleinman RA, Weiss RD. *J Gen Intern Med.* 2022; 37(8): 2103-2109.

BACKGROUND: Despite the focus on overdose deaths co-involving opioids and benzodiazepines, little is known about the epidemiologic characteristics of benzodiazepine-involved overdose deaths in the USA. **OBJECTIVE:** To characterize co-involved substances, intentionality, and demographics of benzodiazepine-involved overdose deaths in the USA from 2000 to 2019.

DESIGN: Cross-sectional study using national mortality records from the National Vital Statistics System. **SUBJECTS:** US residents in the 50 states and District of Columbia who died from a benzodiazepine-involved overdose from 2000 to 2019. **MAIN MEASURES:** Demographic

characteristics, intention of overdose, and co-involved substances. **KEY RESULTS:** A total of 118,208 benzodiazepine-involved overdose deaths occurred between 2000 and 2019 (median age, 43 [IQR, 32-52]; male, 58.6%; White, 93.3%; Black, 4.9%; American Indian and Alaska Native, 0.9%; Asian American and Pacific Islander, 0.9%; Hispanic origin, 6.4%). Opioids were co-involved in 83.5% of the deaths. Nine percent of benzodiazepine-involved overdose deaths did not involve opioids, cocaine, other psychostimulants, barbiturates, or alcohol. Overdose deaths were classified as suicides in 8.5% of cases with benzodiazepine and opioid co-involvement and 36.2% of cases with benzodiazepine but not opioid involvement. Rates of benzodiazepine-involved overdose deaths increased from 0.46 per 100,000 individuals in 2000 to 3.55 per 100,000 individuals in 2017 before decreasing to 2.96 per 100,000 individuals in 2019. Benzodiazepine-involved overdose mortality rates increased from 2000 to 2019 among all racial groups, both sexes, and individuals of Hispanic and non-Hispanic origin. Rates of benzodiazepine-involved overdose deaths decreased among White individuals, but not Black individuals, from 2017 to 2019. **CONCLUSIONS:** Interventions to reduce benzodiazepine-involved overdose mortality should consider the demographics of, co-involved substances in, and presence of suicides among benzodiazepine-involved overdose deaths.

Effects Of A Recombinant Humanized Anti-Cocaine Monoclonal Antibody On The Metabolism And Distribution Of Cocaine In Vitro And In Mice Zinani DB, Turner ME, Wetzel HN, Crutchfield CA, Norman AB. FASEB J. 2022; 36 Suppl 1.

The anti-cocaine monoclonal antibody (mAb), h2E2, is a candidate for treating cocaine-use disorder. h2E2 binds to and sequesters cocaine in the plasma compartment, effectively decreasing cocaine concentrations in the brains of rats and mice. Despite the binding of cocaine to h2E2, plasma cocaine concentrations decline rapidly in rodents over time, but there was a drastic decrease in the urinary elimination of cocaine in the presence of h2E2. Since cocaine is not being renally excreted, the apparent disappearance of cocaine from the plasma must be explained by either metabolism or distribution. However, binding of cocaine to h2E2 may restrict the availability of cocaine for hydrolysis by endogenous esterases. Therefore, the antibody would be expected to extend the elimination half-life of cocaine. In contrast, previous studies reported h2E2 as having no effect on the rate of cocaine clearance. It is important to examine the ultimate clearance of the cocaine to ascertain half-life and potential for re-intoxication. Therefore, we investigated the effects of h2E2 on cocaine hydrolysis in vitro and on cocaine metabolism and disposition in vivo over a six-hour time course. The spontaneous and enzyme-mediated in vitro hydrolysis of cocaine was drastically decreased in the presence of h2E2 in vitro. Additionally, in mice, h2E2 significantly increased the distribution and elimination half-lives of cocaine relative to vehicle controls over an extended time course. Therefore, we concluded that h2E2 slowing the distribution and elimination of cocaine is the most appropriate explanation for the initial disappearance of cocaine from the plasma in vivo.

An Analog Of [d-Trp]CJ-15,208 Exhibits Kappa Opioid Receptor Antagonism Following Oral Administration And Prevents Stress-induced Reinstatement Of Extinguished Morphine Conditioned Place Preference Brice-Tutt AC, Eans SO, Yakovlev D, Aldrich JV, McLaughlin JP. Pharmacol Biochem Behav. 2022; 217: 173405.

Opioid use disorder (OUD) relapse rates are discouragingly high, underscoring the need for new treatment options. The macrocyclic tetrapeptide natural product CJ-15,208 and its stereoisomer [d-Trp]CJ-15,208 demonstrate kappa opioid receptor (KOR) antagonist activity upon oral

administration which prevents stress-induced reinstatement of cocaine-seeking behavior. In order to further explore the structure-activity relationships and expand the potential therapeutic applications of KOR antagonism for the treatment of OUD, we screened a series of 24 analogs of [d-Trp]CJ-15,208 with the goal of enhancing KOR antagonist activity. From this screening, analog 22 arose as a compound of interest, demonstrating dose-dependent KOR antagonism after central and oral administration lasting at least 2.5 h. In further oral testing, analog 22 lacked respiratory, locomotor, or reinforcing effects, consistent with the absence of opioid agonism. Pretreatment with analog 22 (30 mg/kg, p.o.) prevented stress-induced reinstatement of extinguished morphine conditioned place preference and reduced some signs of naloxone-precipitated withdrawal in mice physically dependent on morphine. Collectively, these data support the therapeutic potential of KOR antagonists to support abstinence in OUD and ameliorate opioid withdrawal.

TAAR1 Regulates Drug-induced Reinstatement Of Cocaine-seeking Via Negatively Modulating CaMKII α Activity In The NAc

Liu J, Wu R, Seaman Jr R, Manz KM Johnson B, Vu, J, Huang Y, Zhang Y, Robison AJ, Neve R, Grueter BA, Dietz D, Li J-X. *Mol Psychiatry*. 2022; 27(4): 2136-2145.

Relapse remains a major challenge to the treatment of cocaine addiction. Recent studies suggested that the trace amine-associated receptor 1 (TAAR1) could be a promising target to treat cocaine addiction and relapse; however, the underlying mechanism remains unclear. Here, we aimed to investigate the neural mechanism underlying the role of TAAR1 in the drug priming-induced reinstatement of cocaine-seeking behavior in rats, an animal model of cocaine relapse. We focused on the shell subregion of nucleus accumbens (NAc), a key brain region of the brain reward system. We found that activation of TAAR1 by systemic and intra-NAc shell administration of the selective TAAR1 agonist RO5166017 attenuated drug-induced reinstatement of cocaine-seeking and prevented drug priming-induced CaMKII α activity in the NAc shell. Activation of TAAR1 dampened the CaMKII α /GluR1 signaling pathway in the NAc shell and reduced AMPAR-EPSCs on the NAc slice. Microinjection of the selective TAAR1 antagonist EPPTB into the NAc shell enhanced drug-induced reinstatement as well as potentiated CaMKII α activity in the NAc shell. Furthermore, viral-mediated expression of CaMKII α in the NAc shell prevented the behavioral effects of TAAR1 activation. Taken together, our findings indicate that TAAR1 regulates drug-induced reinstatement of cocaine-seeking by negatively regulating CaMKII α activity in the NAc. Our findings elucidate a novel mechanism of TAAR1 in regulating drug-induced reinstatement of cocaine-seeking and further suggests that TAAR1 is a promising target for the treatment of cocaine relapse.

Glucagon-like Peptide-1 Receptor Agonist, Liraglutide, Reduces Heroin Self-administration And Drug-induced Reinstatement Of Heroin-seeking Behaviour In Rats

Douton JE, Horvath N, Mills-Huffnagle S, Nyland JE, Hajnal A, Grigson PS. *Addict Biol*. 2022; 27(2): e13117.

Drug addiction is a chronic brain disease characterized by the uncontrolled use of a substance. Due to its relapsing nature, addiction is difficult to treat, as individuals can relapse following even long periods of abstinence and, it is during this time, that they are most vulnerable to overdose. In America, opioid overdose has been increasing for decades, making finding new treatments to help patients remain abstinent and prevent overdose deaths imperative. Recently, glucagon-like peptide-1 (GLP-1) receptor agonists have shown promise in reducing motivated behaviours for drugs of abuse. In this study, we test the effectiveness of the GLP-1 analogue, liraglutide (LIR), in reducing heroin addiction-like behaviour, and the potential side effects associated with the treatment. We

show that daily treatment with LIR (0.1 mg/kg sc) increases the latency to take heroin, reduces heroin self-administration, prevents escalation of heroin self-administration and reduces drug-induced reinstatement of heroin-seeking behaviour in rats. A 1-h pretreatment time, however, was too short to reduce cue-induced seeking in our study. Moreover, we showed that, while LIR (0.1, 0.3, 0.6 and 1.0 mg/kg sc) supported conditioned taste avoidance of a LIR-paired saccharin cue, it did not elicit intake of the antiemetic kaolin in heroin-naïve or heroin-experienced rats. Further, 0.1 mg/kg LIR did not produce great disruptions in food intake or body weight. Overall, the data show that LIR is effective in reducing heroin taking and heroin seeking at doses that do not cause malaise and have a modest effect on food intake and body weight gain.

[Smoking Cessation Prevalence And Inequalities In The United States: 2014-2019](#) Leventhal AM, Dai H, Higgins ST. J Natl Cancer Inst. 2022; 114(3): 381-390.

BACKGROUND: Smoking is a leading cause of premature death and health inequities in the United States. **METHODS:** We estimated cross-sectional prevalence of smoking cessation indicators among US adult recent smokers (n = 43 602) overall and by sociodemographic subgroups in the Current Population Survey Tobacco Use Supplement 2014-2015 and 2018-2019 timepoints. Respondents reported past-year quit smoking interest, attempts, sustained (successful) cessation for 6 or more months and use of e-cigarettes or behavioral or pharmacological cessation treatments to quit smoking. **RESULTS:** Past-year quit smoking attempts declined slightly from 2014-2015 (52.9%) to 2018-2019 (51.3%) overall. Quit interest (pooled = 77.1%) and sustained cessation (pooled = 7.5%) did not change across timepoints. Among smokers making past-year quit attempts, 34.4% reported using cessation treatments in 2018-2019, and using e-cigarettes to quit smoking declined from 2014-2015 (33.3%) to 2018-2019 (25.0%). Several non-White (vs White) racial and ethnic groups had higher prevalence of quit interest and attempts but lower prevalence of sustained cessation or using e-cigarettes or treatments to quit. Income, education, employment, and metropolitan residence were positively associated with sustained cessation. Sociodemographic inequalities in sustained cessation and most other outcomes did not change across timepoints. **CONCLUSIONS:** Although about half of US adult smokers made past-year quit attempts from 2014 to 2019, only 7.5% reported sustained cessation, and most who made quit attempts did not report using cessation treatments. Sociodemographic inequalities in cessation were pervasive and not entirely correspondent with sociodemographic variation in motivation to quit. Smoking cessation prevalence and inequalities did not improve from 2014 to 2019. Encouraging quit attempts and equitable access to smoking cessation aids are public health priorities.

HIV RESEARCH

[Methamphetamine Dysregulates Macrophage Functions And Autophagy To Mediate HIV Neuropathogenesis](#) Barbaro JM, Sidoli S, Cuervo AM, Berman JW. Biomedicines. 2022; 10: 1257. HIV-neurocognitive impairment (HIV-NCI) can be a debilitating condition for people with HIV (PWH), despite the success of antiretroviral therapy (ART). Substance use disorder is often a comorbidity with HIV infection. The use of methamphetamine (meth) increases systemic inflammation and CNS damage in PWH. Meth may also increase neuropathogenesis through the functional dysregulation of cells that harbor HIV. Perivascular macrophages are long-lived reservoirs for HIV in the CNS. The impaired clearance of extracellular debris and increased release of reactive oxygen species (ROS) by HIV-infected macrophages cause neurotoxicity.

Macroautophagy is a vital intracellular pathway that can regulate, in part, these deleterious processes. We found in HIV infected primary human macrophages that meth inhibits phagocytosis of aggregated amyloid-increases total ROS and dysregulates autophagic processes. Treatment with widely prescribed ART drugs had minimal effects, although there may be an improvement in phagocytosis when co-administered with meth. Pharmacologically inhibited lysosomal degradation, but not induction of autophagy, further increased ROS in response to meth. Using mass spectrometry, we identified the differentially expressed proteins in meth-treated, HIV-infected macrophages that participate in phagocytosis, mitochondrial function, redox metabolism, and autophagy. Significantly altered proteins may be novel targets for interventional strategies that restore functional homeostasis in HIV-infected macrophages to improve neurocognition in people with HIV-NCI using meth.

Progressive Degeneration And Adaptive Excitability In Dopamine D1 And D2 Receptor-Expressing Striatal Neurons Exposed To HIV-1Tat And Morphine

Lark ARS, Silva LK, Nass SR, Marone MG, Ohene-Nyako M, Ihrig TM, Marks WD, Yarotksyy V, McQuiston AR, Knapp PE and Hauser KF. Cell and Mol Neurobiol. 2022, June 13. Online ahead of print.

The striatum is especially vulnerable to HIV-1 infection, with medium spiny neurons (MSNs) exhibiting marked synaptodendritic damage that can be exacerbated by opioid use disorder. Despite known structural defects in MSNs co-exposed to HIV-1 Tat and opioids, the pathophysiological sequelae of sustained HIV-1 exposure and acute comorbid effects of opioids on dopamine D1 and D2 receptor-expressing (D1 and D2) MSNs are unknown. To address this question, Drd1-tdTomato or Drd2-eGFP-expressing reporter and conditional HIV-1 Tat transgenic mice were interbred. MSNs in ex vivo slices from male mice were assessed by whole-cell patch-clamp electrophysiology and filled with biocytin to explore the functional and structural effects of progressive Tat and acute morphine exposure. Although the excitability of both D1 and D2 MSNs increased following 48 h of Tat exposure, D1 MSN firing rates decreased below control (Tat-) levels following 2 weeks and 1 month of Tat exposure but returned to control levels after 2 months. D2 neurons continued to display Tat-dependent increases in excitability at 2 weeks, but also returned to control levels following 1 and 2 months of Tat induction. Acute morphine exposure increased D1 MSN excitability irrespective of the duration of Tat exposure, while D2 MSNs were variably affected. That D1 and D2 MSN excitability would return to control levels was unexpected since both subpopulations displayed significant synaptodendritic degeneration and pathologic phospho-tau-Thr205 accumulation following 2 months of Tat induction. Thus, despite frank morphologic damage, D1 and D2 MSNs uniquely adapt to sustained Tat and acute morphine insults.

Costs And Impact On HIV Transmission Of A Switch From A Criminalisation To A Public Health Approach To Injecting Drug Use In Eastern Europe And Central Asia: A Modelling

Analysis Ward Z, Stone J, Bishop C, Ivakin V, Eritsyayn K, Deryabina A, Low A, Cepeda J, Kelly SL, Heimer R, Cook R, Altice FL, Litz T, Terlikbayeva A, El-Bassel N, Havarkov D, Fisenka A, Boshnakova A, Klepikov A, Saliuk T, Deshko T, Vickerman P. Lancet HIV. 2022; 9(1): e42-e53.

Background: HIV incidence is increasing in eastern Europe and central Asia, primarily driven by injecting drug use. Coverage of antiretroviral therapy (ART) and opioid agonist therapy are suboptimal, with many people who inject drugs (PWID) being incarcerated. We aimed to assess whether use of monies saved as a result of decriminalization of drug use or possession to scale up ART and opioid agonist therapy could control HIV transmission among PWID in eastern Europe and central Asia. **Methods:** A dynamic HIV transmission model among PWID incorporating

incarceration, ART, and opioid agonist therapy was calibrated to Belarus, Kazakhstan, Kyrgyzstan, and St Petersburg (Russia). Country-specific costs for opioid agonist therapy, ART, and incarceration were collated or estimated. Compared with baseline, the model prospectively projected the life-years gained, incremental costs (2018 euros), and infections prevented over 2020-40 for three scenarios. The decriminalization scenario removed incarceration resulting from drug use or possession for personal use, reducing incarceration among PWID by 24.8% in Belarus, Kazakhstan, and Kyrgyzstan and 46.4% in St Petersburg; the public health approach scenario used savings from decriminalization to scale up ART and opioid agonist therapy; and the full scale-up scenario included the decriminalization scenario plus investment of additional resources to scale up ART to the UNAIDS 90-90-90 target of 81% coverage and opioid agonist therapy to the WHO target of 40% coverage. The incremental cost-effectiveness ratios per life-year gained for each scenario were calculated and compared with country-specific gross domestic product per-capita willingness-to-pay thresholds. Costs and life-years gained were discounted 3% annually.

Findings: Current levels of incarceration, opioid agonist therapy, and ART were estimated to cost from €198 million (95% credibility interval 173-224) in Kyrgyzstan to €4129 million (3897-4358) in Kazakhstan over 2020-40; 74.8-95.8% of these total costs were incarceration costs.

Decriminalization resulted in cost savings (€38-773 million due to reduced prison costs; 16.9-26.1% reduction in overall costs) but modest life-years gained (745-1694). The public health approach was cost saving, allowing each setting to reach 81% ART coverage and 29.7-41.8% coverage of opioid agonist therapy, resulting in 17 768-148 464 life-years gained and 58.9-83.7% of infections prevented. Results were similar for the full scale-up scenario. **Interpretation:** Cost savings from decriminalization of drug use could greatly reduce HIV transmission through increased coverage of opioid agonist therapy and ART among PWID in eastern Europe and central Asia.

[A Community-based Intervention To Decrease The Prevalence Of HIV Viremia Among People Who Inject Drugs In Vietnam](#)

Duong HT, Moles J-P, Pham KM, Vallo R, Hoang GT, Vu VH, Khuat OTH, Nham TTT, Nguyen DQ, Quillet C, Rapoud D, Van De Perre P, Castellani J, Feelemyer J, Michel L, Laureillard D, Jarlais DD, Nagot N. *Lancet Reg Health West Pac.* 2022; 27: 100538.

Background: In most low-to-middle-income countries, HIV control at the population level among people who inject drugs (PWID) remains a major challenge. We aimed to demonstrate that an innovative intervention can identify HIV-positive PWID in the community who are not treated efficiently and get them treated efficiently. **Methods:** Between 2016 and 2020, we implemented an intervention consisting of mass HIV screening of PWID using three annual respondent-driven sampling surveys (RDSS) and a post-intervention evaluation RDSS in community-based organization (CBO) sites, coupled with peer support to facilitate/improve access to antiretroviral and methadone therapy in Haiphong, Vietnam. The primary outcome was the proportion of identified uncontrolled HIV-positive PWID who achieved viral control. We also estimated the potential effect of the intervention on the proportion of PWID with HIV RNA >1000 copies/mL among all PWID during the study period. **Findings:** Over the three RDSS, 3150 different PWID were screened, i.e., two-thirds of the estimated population size. They all injected heroin, their median age was of 39 years, 95% were male, 26.5% were HIV-infected, and 78.6% of the latter had HIV RNA ≤1000 copies/mL. Among the 177 PWID identified with an unsuppressed viral load, 73 (41.2%) achieved viral suppression at the final visit. HIV viremia decreased from 7.2% at baseline to 2.9% at the final RDSS (p<0.001). Up to 42% of this observed reduction may be explained by the intervention, in the absence of any external intervention targeting PWID during the study period.

Interpretation Mass community-based screening using RDSS coupled with CBO support is a powerful tool to rapidly identify untreated HIV-positive PWID and (re)link them to care.

[HIV-Related Drivers Of Sexual Compulsivity And Sexuality In Sexual Minority Men Who Use Methamphetamine](#)

Kondur HR, Lee, TK, McIntosh R, Gouse H, Paul R, Grov C, Fuchs D, Gómez W, Dilworth SE, Neilands TB, Carrico AW. J Neurovirol. 2022 Jul 12. Online ahead of print. Although co-occurring methamphetamine (meth) use and HIV amplify the risk for neuropsychiatric comorbidities, the underlying neuroimmune mechanisms are not well characterized. We examined whether a detectable viral load and dysregulated metabolism of amino acid precursors for neurotransmitters predicted subsequent levels of sexual compulsivity and sexual sensation seeking. This 15-month longitudinal study enrolled 110 sexual minority men (SMM) living with HIV who had biologically confirmed meth use (i.e., reactive urine or hair toxicology results). Peripheral venous blood samples collected at baseline, 6 months, 12 months, and 15 months were used to measure a detectable viral load (> 40 copies/mL), the kynurenine/tryptophan (K/T) ratio, and the phenylalanine/tyrosine (P/T) ratio. The K/T and P/T ratios index dysregulated serotonin and catecholamine (e.g., dopamine) synthesis, respectively. In a cross-lagged panel model, a detectable viral load at 6 months predicted greater sexual compulsivity at 12 months after adjusting for prior levels of sexual compulsivity and recent stimulant use ($\beta = 0.26$, $p = 0.046$). A greater P/T ratio at baseline predicted decreased sexual sensation seeking at 6 months ($\beta = -0.25$, $p = 0.004$) after adjusting for baseline sexual sensation seeking and recent stimulant use. Taken together, HIV replication and dysregulated catecholamine synthesis could potentiate sexual compulsivity while decreasing sexual pleasure in SMM who use meth.

CLINICAL TRIALS NETWORK RESEARCH

[The Association Between Buprenorphine Treatment Duration And Mortality: A Multi-Site Cohort Study Of People Who Discontinued Treatment](#)

Glanz JM, Binswanger IA, Clarke CL, Nguyen AP, Ford MA, Ray GT, Xu S, Hechter RC, Yarborough BJH, Roblin DW, Ahmedani B, Boscarino JA, Andrade SE, Rosa CL, Campbell CI. Addiction. 2022 Jul 11. Online ahead of print.

Background and aims: Buprenorphine is an effective medication for opioid use disorder that reduces mortality; however, many patients are not retained in buprenorphine treatment, and an optimal length of treatment after which patients can safely discontinue treatment has not been identified. This study measured the association between buprenorphine treatment duration and all-cause mortality among patients who discontinued treatment. Secondary objectives were to measure the association between treatment duration and drug overdose and opioid-related overdoses.

Design: Multi-site cohort study. **Setting:** Eight US health systems. **Participants:** Patients who initiated and discontinued buprenorphine treatment between 1 January 2012 and 31 December 2018 ($n = 6550$). Outcomes occurring after patients discontinued buprenorphine treatment were compared between patients who initiated and discontinued treatment after 8-30, 31-90, 91-180, 181-365 and > 365 days. **Measurements:** Covariate data were obtained from electronic health records (EHRs). Mortality outcomes were derived from EHRs and state vital statistics. Non-fatal opioid and drug overdoses were obtained from diagnostic codes. Four sites provided cause-of-death data to identify fatal drug and opioid-related overdoses. Adjusted frailty regression was conducted on a propensity-weighted cohort to assess associations between duration of the final treatment episode and outcomes. **Findings:** The mortality rate after buprenorphine treatment was 1.82 per 100 person-

years (n = 191 deaths). In regression analyses with > 365 days as the reference group, treatment duration was not associated with all-cause mortality and drug overdose (P > 0.05 for both). However, compared with > 365 days of treatment, 91-180 days of treatment was associated with increased opioid overdose risk (hazard ratio = 2.94, 95% confidence interval = 1.11-7.79).

Conclusions: Among patients who discontinue buprenorphine treatment, there appears to be no treatment duration period associated with a reduced risk for all-cause mortality. Patients who discontinue buprenorphine treatment after 91-180 days appear to be at heightened risk for opioid overdose compared with patients who discontinue after > 365 days of treatment.

[Sex Differences In Weight Gain During Medication-Based Treatment For Opioid Use](#)

[Disorder: A Meta-Analysis And Retrospective Analysis Of Clinical Trial Data](#) Manza P, Kroll D, McPherson KL, Johnson A, Dennis E, Hu L, Tai B, Volkow ND. Drug Alcohol Depend. 2022; 238: 109575.

Background: Side effects of medications for opioid use disorder (MOUD) such as weight gain contribute to their stigma. Substantial evidence suggests that women have a more severe side effect profile to MOUD than men, and concerns about weight gain during treatment are prevalent. However, the few studies reporting sex differences in weight gain during treatment show conflicting results and are restricted to methadone. In addition, little is known about possible sex differences in weight gain to buprenorphine, which is the most commonly prescribed MOUD in the United States. **Methods:** To address these issues, we performed a systematic review and meta-analysis on the few studies reporting longitudinal data on sex differences in body mass index (BMI) gain during methadone treatment (Study 1). In a separate study, we also re-analyzed data from trial CTN-0030 of the National Institute on Drug Abuse Clinical Trial Network (NIDA CTN), which involved a 12-week buprenorphine treatment regimen (Study 2; n = 360; 209 Male, 151 Female). **Results:** For Study 1, across all papers reporting longitudinal data (k = 4, n = 362 OUD patients), there were BMI increases that ranged from 2.2 to 5.4 BMI after at least one year of methadone treatment, but there were no significant sex differences in BMI increases (Standardized Mean Difference, Female > Male = 0.352, SE = 0.270; 95 % CI = [-0.18 0.88]; p = .193). Study 2 showed no significant differences in weight before and after 12 weeks of buprenorphine treatment nor did it show sex differences in weight change with treatment ($\beta = 2.34$, p = .511). **Conclusion:** These analyses corroborate evidence of weight gain with methadone treatment but did not observe a sex-based disparity in weight gain with methadone or buprenorphine treatment for OUD.

[Social Determinants Of Mortality Of COVID-19 And Opioid Overdose In American Rural And Urban Counties](#) Zhu Y, Fei Z, Mooney LJ, Huang K, Hser YI. J Addict Med. 2022; 16(1): e52-e55.

Objectives: Both COVID-19 deaths and opioid overdose deaths continue to increase in the United States. Little is known about the characteristics of counties with high rates of mortality for both.

Methods: We analyzed county-level data on COVID-19 mortality from January 1 to May 31, 2020, and on opioid overdose mortality during 2014-2018. The outcome variable, "high-risk county" was a binary indicator of high mortality rates (above 75% quartile) for both COVID-19 and opioid overdose. We conducted geospatial logistic regression models separately for urban and rural counties to identify social determinants of health associated with being a high-risk county.

Results: After adjusting for other covariates, the overall mortality rate of COVID-19 is higher in counties with larger population size and a higher proportion of racial/ethnic minorities, although counties with high rates of opioid overdose mortality have lower proportions of racial/ethnic

minorities, a higher proportion of females, and are more economically disadvantaged. Significant predictors of rural counties with high mortality rates for both COVID-19 and opioid overdose include higher proportions of Blacks (Adjusted odds ratio [aOR], 1.04; 95%CI, 1.01-1.07), American Indians and Alaska Natives (aOR, 1.07; 95%CI, 1.02-1.13), and two or more races (aOR, 1.34; 95%CI, 1.13-1.60). Additional predictors for high-risk urban counties include population density (aOR, 1.12; 95%CI, 1.04-1.22) and higher unemployment rates during the COVID-19 pandemic (aOR, 1.23; 95%CI, 1.07-1.41). **Conclusions:** Rural counties with high proportions of racial/ethnic minorities and urban counties with high unemployment rates are at high mortality risk for COVID-19 and opioid overdose.

Development And Implementation Of A Prescription Opioid Registry Across Diverse Health Systems Ray GT, Altschuler A, Karmali R, Binswanger I, Glanz JM, Clarke CL, Ahmedani B, Andrade SE, Boscarino JA, Clark RE, Haller IV, Hechter R, Roblin DW, Sanchez K, Yarborough BJ, Bailey SR, McCarty D, Stephens KA, Rosa CL, Rubinstein AL, Campbell CI. JAMIA Open. 2022; 5(2): ooac030.

Objective: Develop and implement a prescription opioid registry in 10 diverse health systems across the US and describe trends in prescribed opioids between 2012 and 2018.

Materials and methods: Using electronic health record and claims data, we identified patients who had an outpatient fill for any prescription opioid, and/or an opioid use disorder diagnosis, between January 1, 2012 and December 31, 2018. The registry contains distributed files of prescription opioids, benzodiazepines and other select medications, opioid antagonists, clinical diagnoses, procedures, health services utilization, and health plan membership. Rates of outpatient opioid fills over the study period, standardized to health system demographic distributions, are described by age, gender, and race/ethnicity among members without cancer. **Results:** The registry includes 6,249,710 patients and over 40 million outpatient opioid fills. For the combined registry population, opioid fills declined from a high of 0.718 per member-year in 2013 to 0.478 in 2018, and morphine milligram equivalents (MMEs) per fill declined from 985 MMEs per fill in 2012 to 758 MMEs in 2018. MMEs per member declined from 692 MMEs per member in 2012 to 362 MMEs per member in 2018. **Conclusion:** This study established a population-based opioid registry across 10 diverse health systems that can be used to address questions related to opioid use. Initial analyses showed large reductions in overall opioid use per member among the combined health systems. The registry will be used in future studies to answer a broad range of other critical public health issues relating to prescription opioid use.

Co-Occurring Depression And Suicidal Ideation In Opioid Use Disorder: Prevalence And Response During Treatment With Buprenorphine-Naloxone And Injection Naltrexone Na PJ, Scodes J, Fishman M, Rotrosen J, Nunes EV. J Clin Psychiatry. 2022; 83(3): 21m14140.

Objective: The concept of "deaths of despair" (suicide, overdose, and alcohol-related liver disease) highlights the importance of detecting and understanding the course of co-occurring depression in patients with opioid use disorder (OUD). **Methods:** In a 24-week trial of 570 patients with DSM-5-defined OUD randomized to buprenorphine-naloxone (BUP-NX) or extended-release naltrexone (XR-NTX) from January 2014 to January 2017, the prevalence of depression (assessed with Hamilton Depression Rating Scale [HDRS]) was examined at baseline and after 4 weeks of treatment, and the association between depression and relapse to opioid use was explored using logistic regression. **Results:** Among 473 patients who initiated medication, 14.2% (67/473) had moderate/severe depression ($\text{HDRS} \geq 17$) and 34.9% (165/473) had mild depression ($8 \leq \text{HDRS} \leq 16$)

at baseline. Patients with moderate/severe depression had more frequent histories of anxiety disorders and suicidal ideation. After 4 weeks of treatment, approximately two-thirds of participants with depression either responded (HDRS reduced $\geq 50\%$ from baseline) or remitted (HDRS ≤ 7), with no significant differences between medication treatment groups. Those with moderate/severe depression were less likely to remit (52.8%; 28/53) compared to those with mild depression (76%; 98/129) at week 4 (OR = 0.43, 95% CI = 0.21-0.89, $P = .02$). Further, those who remitted at week 4 had lower, but not significantly different, risk of relapse to opioids compared to those who did not remit (OR = 0.55, 95% CI = 0.28-1.08, $P = .08$). **Conclusions:** Depression is common among patients with OUD and often remits after initiation of BUP-NX or XR-NTX, although when it does not remit it may be associated with worse opioid use outcome. Depression should be screened and followed during initiation of treatment and, when it does not remit, specific depression treatment should be considered. **Trial Registration:** ClinicalTrials.gov identifier: [NCT02032433](https://clinicaltrials.gov/ct2/show/study/NCT02032433).

ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY RESEARCH

Association Of Cyberbullying Experiences And Perpetration With Suicidality In Early

Adolescence Arnon S, Brunstein Klomek A, Visoki E, Moore TM, Argabright ST, DiDomenico GE, Benton TD, Barzilay R. JAMA Netw Open. 2022; 5(6): e2218746.

Importance: Adolescent suicidality (i.e., suicidal ideation or attempts) is a major public health concern. Cyberbullying experiences and perpetration have become increasingly prevalent and are associated with mental health burden, but their roles as independent suicidality risk factors remain unclear. Data are needed to clarify their contribution to teen suicidality to inform suicide prevention efforts.

Objective: To examine whether cyberbullying experiences and perpetration are distinct stressors divergent from other forms of peer aggression experiences in their association with suicidality in early adolescence. **Design, Setting, and Participants:** This cross-sectional analysis used data collected between July 2018 and January 2021 from the Adolescent Brain Cognitive Development (ABCD) study, a large, diverse sample of US children aged 10 to 13 years.

Exposures: Youth reports of cyberbullying experiences or perpetration. **Main Outcomes and Measures:** The main outcome was youth-reported suicidality (past or present, as reported in the ABCD 2-year follow-up assessment). Covariates included demographics, established environmental risk and protective factors for youth suicidality, psychopathology, and experiences or perpetration of offline peer aggression. **Results:** A total of 10,414 ABCD participants were included in this study. Participants had a mean (SD) age of 12.0 (0.7) years and 4962 (47.6%) were female; 796 (7.6%) endorsed suicidality. A total of 930 (8.9%) reported experiencing cyberbullying and 96 (0.9%) reported perpetrating cyberbullying. Of the perpetrators, 66 (69.0%) also endorsed experiencing cyberbullying. Controlling for demographics, experiencing cyberbullying was associated with suicidality (odds ratio [OR], 4.2 [95% CI, 3.5-5.1]; $P < .001$), whereas perpetrating cyberbullying was not (OR, 1.3 [95% CI, 0.8-2.3]; $P = .30$). Experiencing cyberbullying remained associated with suicidality when accounting for negative life events, family conflict, parental monitoring, school environment, and racial and ethnic discrimination (OR, 2.5 [95% CI, 2.0-3.0]; $P < .001$) and when further covarying for internalizing and externalizing psychopathology (OR, 1.8 [95% CI, 1.4-2.4]; $P < .001$). Both being a target and being a perpetrator of offline peer aggression were associated with suicidality (OR, 1.5 [95% CI, 1.1-2.0] for both), controlling for all covariates described earlier. Cyberbullying experiences remained associated with suicidality (OR, 1.7 [95% CI, 1.3-2.2]; $P < .001$, controlling for all covariates) when included with offline peer

aggression experiences and perpetration. **Conclusions and Relevance:** In this cross-sectional study, experiencing—but not perpetrating—cyberbullying was associated with suicidality in early adolescence. This association was significant over and above other suicidality risk factors, including offline peer aggression experiences or perpetration. These findings can inform adolescent suicide prevention strategies, and they suggest that clinicians and educational staff working with this population should routinely evaluate for adolescents' experience with cyberbullying.

[Prenatal Selective Serotonin Reuptake Inhibitor Exposure, Depression, and Brain Morphology In Middle Childhood: Results From The ABCD Study](#) Moreau AL, Voss M, Hansen I, Paul SE, Barch DM, Rogers CE, Bogdan R. *Biological Psychiatry Global Open Science*. 2022 Feb 26. Epub ahead of print.

Background: Prenatal selective serotonin reuptake inhibitor (SSRI) exposure has been inconsistently linked to depression, and little is known about neural correlates. We examined whether prenatal SSRI exposure is associated with depressive symptoms and brain structure during middle childhood. **Methods:** Prenatal SSRI exposure (retrospective caregiver report), depressive symptoms (caregiver-reported Child Behavior Checklist), and brain structure (magnetic resonance imaging–derived subcortical volume; cortical thickness and surface area) were assessed in children (analytic $ns = 5420-7528$; 235 with prenatal SSRI exposure; 9–10 years of age) who completed the baseline Adolescent Brain Cognitive Development Study session. Linear mixed-effects models nested data. Covariates included familial, pregnancy, and child variables. Matrix spectral decomposition adjusted for multiple testing. **Results:** Prenatal SSRI exposure was not independently associated with depression after accounting for recent maternal depressive symptoms. Prenatal SSRI exposure was associated with greater left superior parietal surface area ($b = 145.3 \text{ mm}^2$, $p = .00038$) and lateral occipital cortical thickness ($b = 0.0272\text{mm}$, $p = .0000079$); neither was associated with child depressive symptoms. Child depression was associated with smaller global brain structure. **Conclusions:** Our findings, combined with adverse outcomes of exposure to maternal depression and the utility of SSRIs for treating depression, suggest that risk for depression during middle childhood should not discourage SSRI use during pregnancy. Associations between prenatal SSRI exposure and brain structure were small in magnitude and not associated with depression. It will be important for future work to examine associations between prenatal SSRI exposure and depression through young adulthood, when risk for depression increases.

[Substance Use Onset In High-Risk 9-13 Year-Olds In The ABCD Study](#) Wade NE, Tapert SF, Lisdahl KM, Huestis MA, Haist F. *Neurotoxicol Teratol*. 2022; 91: 107090.

Aim: A key aim of the Adolescent Brain Cognitive DevelopmentSM (ABCD) Study is to document substance use onset, patterns, and sequelae across adolescent development. However, substance use misreporting can obscure accurate drug use characterization. Hair toxicology provides objective historical substance use data but is rarely used in studies of youth. Here, we compare objective hair toxicology results with self-reported substance use in high-risk youth. **Methods:** A literature-based substance use risk algorithm prioritized 696 ABCD Study® hair samples from 677 participants for analysis at baseline, and 1 and 2-year follow-ups (spanning ages 9-13). Chi-square and t-tests assessed differences between participants' demographics, positive and negative hair tests, risk-for-use algorithm scores, and self-reported substance use. **Results:** Hair testing confirmed that 17% of at-risk 9-13 year-olds hair samples had evidence of past 3-month use of one ($n = 97$), two ($n = 14$), three ($n = 2$), or four ($n = 2$) drug classes. After considering prescribed medication and self-reported

substance use, 10% had a positive test indicating substance use that was not reported. Participants with any positive hair result reported less sipping of alcohol ($p < 0.001$) and scored higher on the risk-for-use algorithm ($p < 0.001$) than those with negative toxicology results. **Conclusions:** 10% of hair samples from at-risk 9-13 year-olds tested positive for at least one unreported substance, suggesting underreporting in high-risk youth when participating in a research study. As hair testing prioritized youth with risk characteristics, the overall extent of underreporting will be calculated in future studies. Nonetheless, hair toxicology was key to characterizing substance use in high-risk youth.

Individual-, Peer-, And Parent-Level Substance Use-Related Factors Among 9- And 10-Year-Olds From The ABCD Study: Prevalence Rates And Sociodemographic Differences

Martz ME, Heitzeg MM, Lisdahl KM, Cloak CC, Feldstein Ewing SW, Gonzalez R, Haist F, LeBlanc KH, Madden PA, Megan Ross J, Sher KJ, Tapert SF, Thompson WK, Wade NE. Drug and Alcohol Dependence Reports. 2022; 3: 100037.

Background: Although a relatively large body of research has identified multiple factors associated with adolescent substance use, less is known about earlier substance-related factors during preadolescence, including curiosity to use substances. The present study examined individual-, peer-, and parent-level domains pertaining to substance use and how these domains vary by sociodemographic subgroups and substance type. **Methods:** Participants were 11,864 9- and 10-year-olds from the baseline sample of the Adolescent Brain Cognitive Development (ABCD) Study. Youth-reported measures were curiosity to use substances and perceived peer substance use. Parent-reported measures were availability of and rules about substances. Generalized logistic mixed models (GLMM) were used to compare these measures across alcohol, nicotine, and marijuana and across sociodemographic subgroupings (sex, race/ethnicity, household income, and family history of alcohol problems). GLMM was then used to examine predictors of curiosity to use by substance type. **Results:** The most striking descriptive differences were found between race/ethnicity and income categories (e.g., positive associations between greater income and greater availability of alcohol). In multivariable analyses, greater curiosity to use alcohol was associated with being male, higher household income, perceived peer alcohol use, and easy alcohol availability; greater curiosity to use nicotine was associated with being male, perceived peer cigarette use, easy availability of cigarettes, and no parental rules about cigarette use. **Conclusions:** This study identified substance use-related individual-, peer-, and parent-level factors among a diverse, national sample. Findings highlight the importance of considering sociodemographic and substance-specific variability and may help identify risk and protective factors preceding adolescent substance use.

INTRAMURAL RESEARCH

Brain Lesions Disrupting Addiction Map To A Common Human Brain Circuit Joutsa J, Moussawi K, Siddiqi SH, Abdolahi A, Drew W, Cohen AL, Ross TJ, Deshpande HU, Wang HZ, Bruss J, Stein EA, Volkow ND, Grafman JH, van Wijngaarden E, Boes AD, Fox MD. Nat Med. 2022; 28(6): 1249-1255.

Drug addiction is a public health crisis for which new treatments are urgently needed. In rare cases, regional brain damage can lead to addiction remission. These cases may be used to identify therapeutic targets for neuromodulation. We analyzed two cohorts of patients addicted to smoking at the time of focal brain damage (cohort 1 $n = 67$; cohort 2 $n = 62$). Lesion locations were mapped

to a brain atlas and the brain network functionally connected to each lesion location was computed using human connectome data (n = 1,000). Associations with addiction remission were identified. Generalizability was assessed using an independent cohort of patients with focal brain damage and alcohol addiction risk scores (n = 186). Specificity was assessed through comparison to 37 other neuropsychological variables. Lesions disrupting smoking addiction occurred in many different brain locations but were characterized by a specific pattern of brain connectivity. This pattern involved positive connectivity to the dorsal cingulate, lateral prefrontal cortex, and insula and negative connectivity to the medial prefrontal and temporal cortex. This circuit was reproducible across independent lesion cohorts, associated with reduced alcohol addiction risk, and specific to addiction metrics. Hubs that best matched the connectivity profile for addiction remission were the paracingulate gyrus, left frontal operculum, and medial fronto-polar cortex. We conclude that brain lesions disrupting addiction map to a specific human brain circuit and that hubs in this circuit provide testable targets for therapeutic neuromodulation.

Misconfigured Striatal Connectivity Profiles In Smokers Korponay C, Stein EA, Ross TJ. *Neuropsychopharmacology*. 2022 Jun 25. Epub ahead of print.

Dysregulation of frontal cortical inputs to the striatum is foundational in the neural basis of substance use disorder (SUD). Neuroanatomical and electrophysiological data increasingly show that striatal nodes receive appreciable input from numerous cortical areas, and that the combinational properties of these multivariate "connectivity profiles" play a predominant role in shaping striatal activity and function. Yet, how abnormal configuration of striatal connectivity profiles might contribute to SUD is unknown. Here, we implemented a novel "connectivity profile analysis" (CPA) approach using resting-state functional connectivity data to facilitate detection of different types of connectivity profile "misconfiguration" that may reflect distinct forms of aberrant circuit plasticity in SUD. We examined 46 nicotine-dependent smokers and 33 non-smokers and showed that both dorsal striatum (DS) and ventral striatum (VS) connectivity profiles with frontal cortex were misconfigured in smokers-but in doubly distinct fashions. DS misconfigurations were stable across sated and acute abstinent states (indicative of a "trait" circuit adaptation) whereas VS misconfigurations emerged only during acute abstinence (indicative of a "state" circuit adaptation). Moreover, DS misconfigurations involved abnormal connection strength rank order arrangement, whereas VS misconfigurations involved abnormal aggregate strength. We found that caudal ventral putamen in smokers uniquely displayed multiple types of connectivity profile misconfiguration, whose interactive magnitude was linked to dependence severity, and that VS misconfiguration magnitude correlated positively with withdrawal severity during acute abstinence. Findings underscore the potential for approaches that more aptly model the neurobiological composition of corticostriatal circuits to yield deeper insights into the neural basis of SUD.

Muscarinic Acetylcholine M(2) Receptors Regulate Lateral Habenula Neuron Activity And Control Cocaine Seeking Behavior Wolfe CIC, Hwang EK, Ijomor EC, Zapata A, Hoffman AF, Lupica CR. *J Neurosci*. 2022; 42(28): 5552-5563.

The lateral habenula (LHb) balances reward and aversion by opposing activation of brain reward nuclei and is involved the inhibition of responding for cocaine in a model of impulsive behavior. Previously, we reported that the suppression of cocaine seeking was prevented by LHb inactivation or nonselective antagonism of LHb mAChRs. Here, we investigate mAChR subtypes mediating the effects of endogenous acetylcholine in this model of impulsive drug seeking and define cellular mechanisms in which mAChRs alter LHb neuron activity. Using *in vitro* electrophysiology, we find

that LHb neurons are depolarized or hyperpolarized by the cholinergic agonists oxotremorine-M (Oxo-M) and carbachol (CCh), and that mAChRs inhibit synaptic GABA and glutamatergic inputs to these cells similarly in male and female rats. Synaptic effects of CCh were blocked by the M₂-mAChR (M₂R) antagonist AFDX-116 and not by pirenzepine, an M₁-mAChR (M₁R) antagonist. Oxo-M-mediated depolarizing currents were also blocked by AFDX-116. Although M₂R activation inhibited excitatory and inhibitory inputs to LHb neurons, the effect on excitation was greater, suggesting a shift in excitatory-inhibitory balance toward net inhibition. Activation of VTA inhibitory inputs to LHb neurons, via channelrhodopsin-2 expression, evoked IPSCs that were inhibited by M₂Rs. Finally, we measured LHb-dependent operant response inhibition for cocaine and found it impaired by antagonism of M₂Rs, and not M₁Rs. In summary, we show that a cholinergic signal to LHb and activation of M₂Rs are critical to enable inhibition of responding for cocaine, and we define cellular mechanisms through which this may occur. **Significance Statement:** The lateral habenula (LHb) is a brain region receiving information from brain areas involved in decision-making, and its output influences motivation, reward, and movement. This interface between thoughts, emotions, and actions is how the LHb permits adaptive behavior, and LHb dysfunction is implicated in psychiatric and drug use disorders. Silencing the LHb impairs control over cocaine seeking in rats, and mAChRs are also implicated. Here, we measured cocaine seeking while blocking different mAChRs and examined mechanisms of mAChR effects on LHb neurons. M₂-mAChRs were necessary for control of cocaine seeking, and these receptors altered LHb neuron activity in several ways. Our study reveals that LHb M₂-mAChRs represent a potential target for treating substance use disorders.

[Reversing Anterior Insular Cortex Neuronal Hypoexcitability Attenuates Compulsive Behavior In Adolescent Rats](#) Jadhav KS, Bernheim AP, Aeschlimann L, Kirschmann G, Decosterd I, Hoffman AF, Lupica CR, Boutrel B. Proc Natl Acad Sci U S A. 2022; 119(21): e2121247119.

Development of self-regulatory competencies during adolescence is partially dependent on normative brain maturation. Here, we report that adolescent rats as compared to adults exhibit impulsive and compulsive-like behavioral traits, the latter being associated with lower expression of mRNA levels of the immediate early gene *zif268* in the anterior insula cortex (AIC). This suggests that underdeveloped AIC function in adolescent rats could contribute to an immature pattern of interoceptive cue integration in decision making and a compulsive phenotype. In support of this, we report that layer 5 pyramidal neurons in the adolescent rat AIC are hypoexcitable and receive fewer glutamatergic synaptic inputs compared to adults. Chemogenetic activation of the AIC attenuated compulsive traits in adolescent rats supporting the idea that in early stages of AIC maturity there exists a suboptimal integration of sensory and cognitive information that contributes to inflexible behaviors in specific conditions of reward availability.

[Target Deconvolution Studies Of \(2R,6R\)-Hydroxynorketamine: An Elusive Search](#)

Bonaventura J, Gomez JL, Carlton ML, Lam S, Sanchez-Soto M, Morris PJ, Moaddel R, Kang HJ, Zanos P, Gould TD, Thomas CJ, Sibley DR, Zarate CA Jr, Michaelides M. Mol Psychiatry. 2022 Jun 29. Epub ahead of print.

The off-label use of racemic ketamine and the FDA approval of (S)-ketamine are promising developments for the treatment of depression. Nevertheless, racemic ketamine and (S)-ketamine are controlled substances with known abuse potential and their use is associated with undesirable side effects. For these reasons, research efforts have focused on identifying alternatives. One candidate

is (2R,6R)-hydroxynorketamine ((2R,6R)-HNK), a ketamine metabolite that in preclinical models lacks the dissociative and abuse properties of ketamine while retaining its antidepressant-like behavioral efficacy. (2R,6R)-HNK's mechanism of action however is unclear. The main goals of this study were to perform an in-depth pharmacological characterization of (2R,6R)-HNK at known ketamine targets, to use target deconvolution approaches to discover novel proteins that bind to (2R,6R)-HNK, and to characterize the biodistribution and behavioral effects of (2R,6R)-HNK across several procedures related to substance use disorder liability. We found that unlike (S)- or (R)-ketamine, (2R,6R)-HNK did not directly bind to any known or proposed ketamine targets. Extensive screening and target deconvolution experiments at thousands of human proteins did not identify any other direct (2R,6R)-HNK-protein interactions. Biodistribution studies using radiolabeled (2R,6R)-HNK revealed non-selective brain regional enrichment, and no specific binding in any organ other than the liver. (2R,6R)-HNK was inactive in conditioned place preference, open-field locomotor activity, and intravenous self-administration procedures. Despite these negative findings, (2R,6R)-HNK produced a reduction in immobility time in the forced swim test and a small but significant increase in metabolic activity across a network of brain regions, and this metabolic signature differed from the brain metabolic profile induced by ketamine enantiomers. In sum, our results indicate that (2R,6R)-HNK does not share pharmacological or behavioral profile similarities with ketamine or its enantiomers. However, it could still be possible that both ketamine and (2R,6R)-HNK exert antidepressant-like efficacy through a common and previously unidentified mechanism. Given its pharmacological profile, we predict that (2R,6R)-HNK will exhibit a favorable safety profile in clinical trials, and we must wait for clinical studies to determine its antidepressant efficacy.

GRANTEE HONORS AND AWARDS

Brian Ahmedani, Ph.D., M.S.W., Henry Ford Health, has been chosen to receive the American Foundation for Suicide Prevention Annual Research Award.

James C. Anthony, Ph.D., Michigan State University, received the Society for Prevention Research's Presidential Award at the Society's 2022 Annual Meeting.

Trenette Clark Goings, Ph.D., University of North Carolina, received the Society for Prevention Research's Advances in Culture and Diversity in Prevention Science Award at the Society's 2022 Annual Meeting.

Kevin Haggerty, Ph.D., University of Washington, was named a fellow of the Society for Prevention Research at the annual meeting in June 2022.

Yasmin Hurd Ph.D., Professor, Icahn School Medicine at Mount Sinai, has been elected to the National Academy of Sciences.

Leslie Leve, Ph.D., University of Oregon, was named a 2022 fellow of the Society for Prevention Research at the Annual Meeting in June.

Russ Poldrack, Ph.D., Stanford University, won the Organization for Human Brain Mapping Open Science Award, which recognizes an individual or team's sustained and impactful efforts in the area of open science.

Eric Strain, M.D., Johns Hopkins University School of Medicine, was awarded the Martin and Toby Adler Distinguished Service Award at the College on Problems of Drug Dependence (CPDD) 2022 meeting.

STAFF HONORS AND AWARDS

Aketzali Garcia Gutierrez, Ph.D., was awarded the Scientific Director's Fellowship for Diversity in Research.

Evan Hart, Ph.D., was awarded a K99-BRAIN Initiative Advanced Postdoctoral Career Transition Award to Promote Diversity entitled "Probing the mechanisms and circuits underlying orbitofrontal signaling."

CDR Keisher Highsmith, Dr.PH, Officer in the U.S. Public Health Service Commissioned Corps, received the Hubert H. Humphrey Award for Service to America.

Thorsten Kahnt, Ph.D., Chief, Learning and Decision-Making Unit, NIDA Intramural Research Program (IRP), received the Association for Chemoreception Sciences (AChemS) Young Investigator Award for Research in Olfaction or Nasal Chemosensation.

2022 NIDA IRP Mentoring Awardees

- **Katherine Savell, Ph.D.:** Postdoctoral Fellow Mentoring Award
- **Shiliang Zhang, Ph.D.:** Staff Scientist Mentoring Award
- **Brenda Curtis, Ph.D.:** Investigator Mentoring Award
- **Brenda Curtis, Ph.D.:** Diversity Mentoring Award

NIDA IRP 2023 Fellows Award for Research Excellence (FARE) Awardees

- **Albert Burgess-Hull, Ph.D.**
- **Briana Hempel, Ph.D.**
- **Brenton Laing, Ph.D.**
- **Andras Leko, Ph.D.**
- **David Reiner, Ph.D.**
- **Rani Richardson, Ph.D.**
- **Omar Soler-Cedeno, Ph.D.**
- **Caleb Vogt, Ph.D.**

NIH Center on Compulsive Behaviors (CCB) Fellowship Awardees

- **Andras Leko, Ph.D.** (new)
- **Zilu Ma, Ph.D.** (new)
- **Katherine Savell, Ph.D.** (new)
- **Tingting Liu, Ph.D.** (new)
- **Brenton Laing, Ph.D.** (renewal)
- **Yosuke Arima, Ph.D.** (renewal)
- **Nicholas Beacher, Ph.D.** (renewal)
- **Ying Duan, Ph.D.** (renewal)
- **Briana Hempel, Ph.D.** (renewal)
- **Marios Panayi, Ph.D.** (renewal)
- **Coleman Calva, Ph.D.** (renewal)

STAFF CHANGES

New Staff/Appointments

Diana Alkire, Ph.D., has joined NIDA's Division of Extramural Research (DER) as a Program Analyst for the ABCD Study. She earned her Ph.D. in Neuroscience and Cognitive Science from the University of Maryland, College Park (UMCP), where she conducted research on social cognition (e.g., theory of mind) in autistic and typically developing youth using varied methods, including functional MRI and behavioral observation coding. Diana continued this work during her postdoctoral training at UMCP, where she also contributed to the design and implementation of a longitudinal study of the biopsychosocial predictors of loneliness in autistic and typically developing adolescents.

Jeremiah Bertz, Ph.D., joined the NIDA Center for the Clinical Trials Network (CCTN) on July 18, 2022. He will serve as a Health Scientist Administrator to assist in the implementation of CTN operations and as a Scientific Officer for CTN studies. Dr. Bertz comes to us from the NIDA IRP, where he was a staff scientist in the Office of the Clinical Director. He earned his Ph.D. in psychology from the University of Michigan, where he studied the motivational effects of opioid-associated stimuli in animals under the mentorship of James Woods, Ph.D. After further preclinical training as a post-doctoral fellow in pharmacology at the University of Michigan Medical School, he transitioned to clinical research at the NIDA IRP as a post-doctoral fellow under the mentorship of Kenzie Preston, Ph.D., and David Epstein, Ph.D. At the IRP, his work focused on opioid use disorder treatment outcomes, including assessments of daily life during opioid agonist treatment by various mobile/wearable technologies. His research also involved designing and implementing translational human laboratory studies and clinical trials of behavioral interventions for people with opioid use disorder and people who drink alcohol.

Heather Boerner, M.S., joined the Communications Branch, OSPC, as a Technical Writer/Editor in August 2022. Heather writes evidence-based communications on stigmatized health conditions and scientific research. Before joining NIDA, Heather had a 25-year career as a newspaper, magazine and online journalist and author, most recently covering HIV. Her work has appeared in NPR, PBS NewsHour, *The Washington Post*, The Daily Beast, and TheBody and TheBodyPRO, among others. An excerpt of her book on HIV and pregnancy (which overlaps with substance use disorders), was published in *The Atlantic*. Heather also has experience with in-house communications, as she consulted for Genentech for a decade to assist the company in storytelling about its diversity, equity, and inclusion goals. She has a master's in journalism from Columbia University and is originally from Southern California, but now calls Pittsburgh home, and will be working remotely.

Kathleen Borgmann, Ph.D., recently joined NIDA as a Program Officer in the Genetics, Epigenetics, Development Branch of the Division of Neuroscience and Behavior (DNB). Kathleen comes to us from the University of Texas Health Science Center in Fort Worth, Texas where she was an Assistant Professor. She led a research program that focused on the role of glial inflammation in neurodegeneration, particularly in the context of HIV/AIDS, substance use disorders, and dementias. Her research identified a novel receptor for methamphetamine in astroglia that regulates the functions of these cells, including endoplasmic reticulum/mitochondrial

stress responses and excitatory neurotransmitter clearance from the tripartite synapse. Other research areas included investigating changes in exosome signaling in response to neuroinflammation and SARS-CoV-2 infection, latent HIV infection, and the TIMP-1/MMP balance in human astroglia. Through her clinical research she identified several biomarkers for HIV-associated neurocognitive disorders. Kathleen earned her Ph.D. in Biomedical Sciences at the University of Texas Health Science Center, under the mentorship of Anuja Ghorpade, Ph.D., and was promoted to Assistant Professor in 2019. Kathleen will work with other DNB program staff in the development and guidance of a growing portfolio focused on the interaction of HIV, drugs, and substance use disorders.

Tom Clarke, Ph.D., M.P.H., joined NIDA in August 2022 as Deputy Director of the Office of Science Policy and Communications (OSPC). Tom came to NIDA from the Substance Abuse and Mental Health Services Administration (SAMHSA), where he most recently served as the Director of the National Mental Health and Substance Use Policy Laboratory and Acting Deputy Director for the Center for Behavioral Health Statistics and Quality. During Tom's tenure at SAMHSA, he held leadership roles focused on policy, program, and data analysis in the areas of substance use prevention, treatment, and mental health. Prior to SAMHSA, Tom was a Policy Analyst at the Government Accountability Office via the Pathways Program, where he developed guidance on methodological approaches for evaluating federal programs. Tom has also worked in the non-profit sector on global health initiatives focused on HIV prevention and treatment. He earned a Master of Public Health from the University of Michigan and a doctorate in the Social Behavioral Sciences from the University of Arizona.

Jana Drgonova, Ph.D., joined the Clinical Medical Branch, Division of Therapeutics and Medical Consequences (DTMC), as a Health Scientific Administrator. Jana earned a M.S. in Biotechnology and a Ph.D. in Biochemistry from the Slovak Technical University of Slovakia. Prior to joining NIDA, she was a Fogarty Fellow from 1995 to 1999 at the National Institute of Diabetes and Digestive and Kidney Diseases. Subsequently, Jana became a staff fellow and staff scientist at NIDA IRP, where she worked in the Genetics and Molecular Biology of Addiction Program of George Uhl, Ph.D. She conducted multiple preclinical studies that encompassed biochemistry, molecular biology, genetics, and behavioral pharmacology. Jana also has extensive experience conducting preclinical studies of toxicology, pharmacokinetics, and drug interaction. She subsequently worked as a Scientific Review officer at the Center for Scientific Review before moving to the Veterans Administration (VA), where she served as a Scientific Program Manager. At the VA, Jana managed three research portfolios: Neurobiology and Addictive Disorders; Preclinical Mental Health; and the Neurobiology of Algesia, Analgesia and Analgesic Tolerance. She joined NIDA in July 2022.

Lennin Greenwood joined NIDA's DER as a Grants Management Specialist on April 10, 2022.

Elyse Grossman, Ph.D., JD, MPP, joined the Division of Epidemiology, Services and Prevention Research (DESPR), Epidemiology Research Branch, as a Program Official where her programmatic interests will include evaluating and understanding drug markets and the impact of drug-related laws.

August Holtyn, Ph.D., joined the NIDA CCTN on June 20, 2022. As a Health Scientist Administrator, August assists with the implementation of CTN operations and serves as a Scientific Officer for CTN studies. August is a behavioral pharmacologist with research experience spanning preclinical medications development and outpatient therapeutic trials. She comes to us from the Department of Psychiatry and Behavioral Sciences at the Johns Hopkins University School of Medicine, where she served as the Associate Director of the Center for Learning and Health. August earned her master's and doctoral degrees in psychology at West Virginia University under the mentorship of Michael Perone, Ph.D. In 2015, she joined the faculty in the Johns Hopkins University School of Medicine after completing a post-doctoral fellowship there in behavioral pharmacology under the mentorship of Kenneth Silverman, Ph.D. Her prior work has focused on the development and evaluation of behavioral treatment interventions emphasizing therapeutic use of financial incentives, the integration of behavioral (e.g., contingency management) and pharmacological (e.g., naltrexone) interventions, and the use of technology to facilitate delivery of behavioral and pharmacological treatments for substance use disorders.

Matt Houle joined NIDA's Office of Management as an Ethics Specialist on June 6, 2022.

Shkeda Johnson, M.P.A., has been selected as NIDA's Deputy Executive Officer. Prior to coming to NIDA, Shkeda had been with the National Heart, Lung and Blood Institute (NHLBI) since 2013. Her most recent position at NHLBI was Director of the NHLBI Office of Workforce Development and Support. In that role, she oversaw the enterprise people support function including development, innovative learning, performance management, awards and recognition, retention, employee engagement and diversity and inclusion. In her prior role, Shkeda served as the NHLBI Chief Administrative Officer. Prior to joining the NIH, Shkeda worked in key roles at the Administration for Children and Families, as Chief of Staff to the Deputy Assistant Secretary for Administration, and at the Health Resources and Services Administration, her first position upon graduating from the Department of Health and Human Services Emerging Leader's Fellowship Program. Shkeda holds a Master of Public Administration degree and a Bachelor of Science/Political Science degree. As a lifelong learner, she has received certificates from the Federal Executive Institute, Harvard Executive Education Program, and Georgetown University School of Continuing Education.

Judith Lavelle, M.S., has been selected as the new supervisory public affairs specialist leading the content team in OSPC's Communication Branch, effective August 28. Judy joined NIDA in 2020 as OSPC's content team lead, and in her two-year tenure has made impressive contributions to NIDA's communication of health information. Judy has developed a comprehensive strategy to update NIDA's online content with information that accurately informs the public about today's complex drug environment—including polydrug use, fentanyl contamination, overdoses, and harm reduction. Judy is an accomplished science writer and editor and has a solid grounding on press relations from her four years at the National Institute of Allergy and Infectious Diseases. In this role, she communicated HIV science. Judy has also served as a reporter for *Chemical & Engineering News*. She was a member of Phi Beta Kappa at Wells College and has a Master of Science degree in Science Journalism from Boston University.

Josh Lazarus, a Contract Specialist at NIDA, was promoted to supervisory Contracting Officer for the NIDA Section in the Office of Acquisitions on July 30, 2022.

Angela Lee-Winn, Ph.D., joined DESPR's Prevention Research Branch (PRB) in July 2022. Angela will also be working with the Services Research Branch, covering HIV related portfolios for both Branches.

Feng Li, Ph.D., has joined the Chemistry and Pharmaceutics Branch, DTMC, as a program officer specializing in formulation and drug-delivery systems for the treatment of substance use disorders. Feng was trained as a pharmaceutical scientist with broad knowledge of drug formulation, pharmaceutics, biopharmaceutics, and pharmacokinetics. Prior to joining NIDA, Feng worked as a faculty member in universities for 11 years and served as the PI or co-PI of multiple research projects funded by NIH and other agencies. He joined NIDA in May 2022.

Tristan McClure-Begley, Ph.D., joined NIDA in May 2022 as the new Chief of the Integrative Neuroscience Branch in the Division of Neuroscience and Behavior. Tristan previously served as a Program Manager in the Biological Technologies Office of the Defense Advanced Research Projects Agency (DARPA) since 2017. His scientific breadth and depth span many fields including molecular biology, proteomics, pharmaceutical chemistry, psychology, and neuroscience. His scientific pursuits at DARPA have involved novel chemical biology approaches to treating disease and injury and developing methods to accelerate and protect learning and executive functions. Examples of innovative programs he developed at DARPA include: the Biostasis program, which leverages pharmacological chaperoning to protect biological systems for trauma care; the Panacea program in systems pharmacology for understanding the human interactome for pain and stress; the Focused Pharma program to accelerate treatments for neuropsychiatric conditions; and the Assessing Immune Memory program to understand mechanisms of persistent immunity. Tristan came to DARPA from the University of Colorado, Boulder, where he was a Research Assistant Professor in the Department of Molecular, Cellular and Developmental Biology. His academic studies focused on molecular mechanisms of perturbations to complex biological systems, particularly drugs of abuse, toxins, and neurodevelopmental disorders. Prior to his faculty position, Tristan was a postdoctoral fellow in the laboratory of Marina Picciotto, Ph.D., in the Department of Psychiatry at the Yale University School of Medicine, and an alumnus of the Yale/NIDA Neuroproteomics Center. He received his Doctor of Philosophy degree in Integrative Physiology and a Graduate Certificate in Behavioral Genetics from the University of Colorado, Boulder.

Traci M. Murray, Ph.D., M.P.H., RN, NHDP-BC, CPH, is a Lieutenant Commander in the United States Public Health Service. She joins NIDA's DER as a Scientific Advisor for Justice, Equity, Diversity, and Inclusion for the ABCD and HEALthy Brain and Child Development studies. Traci has been a registered nurse for more than 10 years and has experience in clinical research, epidemiology, and nursing education. She earned her Bachelor of Science in Nursing with honors from Texas Christian University, her PhD at University of Texas at Tyler, and her Master of Public Health degree at University of North Texas Health Science Center. Traci spent nearly three years with the Indian Health Service serving the Winnebago Tribe of Nebraska and Navajo Nation in various clinical and administrative roles. She most recently served as Assistant Regional Administrator for SAMHSA in Dallas, where she created and led several initiatives. These included the national Partnerships for Equity initiative to address behavioral health inequities through innovative cross-agency partnerships, as well as The Yard, an internal diversity initiative for historically black colleges and universities alumni and other interested staff.

Valery Rodrigue has joined NIDA's Financial Management Branch (FMB) as a Budget Analyst. Valery is a Management Intern with the NIH Training Center under the Office of the Director and is joining FMB for a four month rotation. Over the next two years, she will rotate through different administrative career fields at NIH and NIDA. Prior to joining the Management Intern program, Valery worked with the NIH Clinical Center for more than 13 years as a Senior Clinical Research Nurse with the Clinical Center Nursing Department under the Oncology and Critical Care Services. In 2018, she transitioned to the NIH Clinical Center Office of Patient Recruitment, which is part of the Office of Communications and Media Relations. As a Patient Recruitment Specialist, Valery's love of people engendered her active participation in community engagements, outreach events, and public health initiatives. Valery earned a Bachelor of Science degree in nursing from Northeastern University College of Nursing in Boston, Massachusetts. While she is with FMB, Valery will be focused on a wide range of duties and special projects and looks forward to working with the team.

Melba Rojas joined NIDA Office of Management's Office of the Director as an Ethics Specialist on July 5, 2022.

Allisen Stewart, M.A., joined the Communications Branch, OSPC, in June of 2022. She began her NIH career as a summer student and became a full-time employee after graduating from college. In 2003, she graduated from NIH Management Intern Program and has since worked at multiple NIH Institutes as a technical writer/editor and digital information specialist overseeing web analysis and Section 508 maintenance. At NIDA, Allisen is responsible for managing web analytics, updating and maintaining content on the NIDA website, and managing email-based outreach. Allisen is enthusiastic about NIH's mission to provide science-based, health information to everyone. Allisen received a B.A. from Virginia Tech and an M.A. degree in Government from Johns Hopkins University.

Drew Townsend, Ph.D., recently joined the Medications Discovery and Toxicology Branch of DTMC, as a Health Scientist Administrator. Drew earned a B.A. in Psychology and a Ph.D. in Neurosciences at the University of Mississippi. He completed a post-doctoral fellowship with Matthew Banks, Ph.D., at Virginia Commonwealth University in Richmond, Virginia. He is an accomplished behavioral pharmacologist with experience evaluating drugs of abuse and medications in rodents and nonhuman primates with a focus on medications development. Drew was a co-investigator on several NIH funded grants and published on using behavioral models to evaluate potential opioid vaccines and antinociceptive agents in the context of reward and abuse potential. Prior to joining NIDA, Drew was an Assistant Professor in the Department of Pharmacology and Toxicology at the Virginia Commonwealth University. His experience corresponds well with DTMC's programmatic needs, especially the Addiction Treatment Discovery Program, where his behavioral pharmacology experience will make him an immediate asset.

Claudia Ventola joined NIDA's Office of Management's Office of Acquisitions as a Contract Specialist on June 19, 2022.

Erica Wells joined NIDA's DER as a Supervisory Grants Management Specialist on April 10, 2022.

Staff Departures

Jessica McQueen, Ph.D., a Health Scientist Administrator in the NIDA DER Office of the Director, left NIDA on May 21, 2022, for a position with the National Center for Complementary and Integrative Health.

Minna Liang, Ph.D., PMP, a Health Scientist Administrator Referral Officer in the NIDA DER Office of the Director left NIDA on May 21, 2022, for a position with the NIH Office of the Director.

Anna Wheeler, an Ethics Coordinator in NIDA's Office of Management's Office of the Director, left NIDA on June 4, 2022, for a position in the NIH's Office of General Council.

Retirements

Charlotte Annan, an Administrative Technician on NIDA's Office of Management's Red Team, retired from Federal service on June 30, 2022.

Elaine Solano, an Extramural Support Assistant in NIDA's CCTN, retired from Federal Service on September 2, 2022.

Robert (Bob) Walsh, Chief, Regulatory Affairs Branch, DTMC, retired on May 31, 2022, after more than 35 years of Federal service at NIDA. Bob began his career at NIDA on March 1, 1987, in the Research Technology Branch, Division of Preclinical Research as a chemist, where he directed the NIDA Drug Supply Program and NIDA's marijuana farm. Bob was one of the founding members of NIDA's Medications Development Division (MDD) serving in the Chemistry and Pharmaceutics Branch. Bob made major contributions to the following New Drug Application (NDA) projects: LAAM, Subutex (buprenorphine), Suboxone (buprenorphine/naloxone), lofexidine, and nasal naloxone.

Mark Coggiano retired in June 2022 from the IRP's Medications Development Program.



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